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PULMONARY TUBERCULOSIS AS A PART OF A SYSTEMIC INFECTION (HEMATOGENOUS PULMONARY TUBERCULOSIS) *

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INTRODUCTION

IT is my belief that among general practitioners of medicine pulmonary tuberculosis is usually regarded as a local disease of the lung, produced by the inhalation of tubercle bacilli, and that their ideas of hematogenous tuberculosis are restricted to that form of the disease which we recognize as general miliary tuberculosis.

In the light of modern knowledge these are limited and crude concepts of this disease, which greatly hamper our proper appreciation of many important problems concerning its etiology, pathogenesis, clinical manifestations, prevention and treatment.

It is my present purpose to review the evidence demonstrating that pulmonary tuberculosis is very frequently a part of a systemic infection, in the hope that this may help to clarify our ideas of this important subject.

One of the important objects to be obtained from such a review would be the appreciation of the relationship between first infection with tuberculosis, which usually occurs in early life, and the serious forms of pulmonary tuberculosis which as a rule occur in adult life. In doing so, we will also have occasion to consider the possible desirability of modifying the classifications of pulmonary tuberculosis now in general use in this country.

HISTORICAL REVIEW

When Koch first discovered the tubercle bacillus he believed that phthisis was the direct result of a first infection of the lungs with tubercle bacilli. This continued to be the general concept up to the early part of the present century, and Cornet's [1] handbook on tuberculosis, published in 1904, which was recognized as authority at that time, expresses this view. But it is significant that in this same year of 1904 von Behring [2] announced his famous dictum: "Adult phthisis is the last tune of a cradle song." But even before that, Petruschky [3] and Hamburger [4] had thought of tuberculosis

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as a chronic smouldering infection, and Hamburger particularly, as a pediatrician, classified his cases into early and late forms of the disease. Following the rediscovery and the appreciation of the significance of the primary complex by Albrecht [5] and particularly by Ghon [6] in 1912, Ranke [7] in 1916 built up a very imposing structure about the three-stage evolution of tuberculosis, based upon the theory of blood stream dissemination modified by his ideas of the various states of allergy. Ranke was the first definitely to clarify the idea of phthisis as a final phase of a systemic tuberculous disease which has become localized in the organs, particularly the lungs. In the meantime Marmorek [8] had demonstrated that tubercle bacilli reach the blood stream within a few hours after the first infection, and Liebermeister [9] had proved conclusively that bacillemia frequently occurs in tuberculous patients. In recent years Löwenstein [10] has made extravagant claims of the demonstration of tubercle bacilli in the blood, which have not been corroborated by other workers. But the conservative opinion of Wilson [11] that bacillemia occurs in about 5 per cent of all patients, and as a transitory phenomenon perhaps much more frequently, is becoming more and more generally accepted.

It is interesting to note that French clinicians in general have always leaned to the idea of pulmonary tuberculosis as a part of a systemic infection. Landouzy [12] coined the term "typho-bacillose" and arrived at his conclusion as to the tuberculous origin of idiopathic pleural effusions because of this point of view. Bard [13] and Piéry [14] built up a most admirable classification of pulmonary tuberculosis upon this basis, and the more modern phthisiologists such as Rist,[15] Sergent,[16] Bernard,[17] Bezançon [18] all assume that pulmonary tuberculosis frequently represents the extension of a systemic infection to the lungs.

In England, Wingfield [19] has recently offered some very keen observations in support of the concept of the hematogenous origin and evolution of many cases of phthisis.

It is, however, from Germany that the chief recent additions to our knowledge have come. Beginning with Koch, followed by Orth,[20] Roemer [21] and many other experimenters, the idea that phthisis was due to a reinfection rather than to a primary infection was gradually developed. But while the possibility that this reinfection was endogenous was recognized, under the influence of Aschoff [22] there was gradually built up the strongly entrenched theory that pulmonary phthisis is due to a new exogenous infection entirely independent of the first infection. The influence of Aschoff and his associates has been very great, and since his visit to this country his ideas have largely dominated American medical thought concerning the pathogenesis of phthisis.

But in the past 10 or 15 years, pathologists and clinicians alike in Germany have been very definitely swinging around to a critical attitude toward Aschoff's ideas. Redeker,[23] Loeschcke,[24] Duken,[25] Schürmann,[26] Pagel,[27] Rüdel,[28] and Neumann [29] in Vienna all have been stressing patho-

logical and clinical evidence in favor of the close relationship between the first infection and the phthisis which results so many years later.

Thus, the issue is drawn between the advocates of exogenous reinfection as the cause of phthisis and those that believe in the endogenous sources of such reinfection.

It should be emphasized, however, that no one doubts that exogenous reinfection occurs and is probably quite frequent. On the other hand, it is becoming more and more the accepted idea that the endogenous sources of reinfection have been improperly relegated to the background and are of very marked, if not indeed of predominant, importance.

Pathogenesis of Tuberculosis

Primary Infection. The primary infection with tuberculosis occurs usually in the lungs, but occasionally elsewhere in the body, particularly the intestinal tract. The original lesion which is produced is usually slight and most frequently is unaccompanied by symptoms. Sometimes, however, it is quite extensive and accompanied by acute symptoms. Associated with the lung lesion there is invariably an accompanying lesion of the neighboring lymph nodes, which in the case of the lungs are the tracheobronchial group. As a rule, these two conjoined lesions become rather quickly quiescent and tend to become calcified, in which phase they are ordinarily recognized either by the roentgenogram during life or by postmortem examination. These two conjoined primary lesions in the lungs and lymph nodes have received the designation of the primary complex.

After this first infection occurs there is a changed reaction in all of the tissues of the body toward tuberculo-protein, which gives rise to the well known sensitization to tuberculin and which definitely changes and tends to localize the tissue reaction to any secondary tuberculous infection which may occur whether from without, which is termed exogenous reinfection, or by dissemination from the original lesion, which is termed endogenous reinfection.

The course of the primary infection itself is variable. The disease may spread acutely from this first infection and rapidly cause death, particularly in young children. Most commonly, however, the lesions subside and become calcified and give no symptoms.

In a considerable number of cases, after a long period of quiescence these lesions which are caseating and partly calcified may discharge tubercle bacilli into the blood stream in varying amounts and at varying intervals. This discharge of bacilli occurs particularly from the lymph nodes. We know that actual pathological healing of these lymph node lesions is very uncertain; even when they appear perfectly calcified they may contain virulent bacilli which may be discharged into the blood. It is from this source that the various forms of hematogenous tuberculosis occur, including certain forms of pulmonary tuberculosis which will be our chief concern in this paper.

Post-Primary Disseminations. The discharges of tubercle bacilli from the original primary lesions may occur early or late, often many years after the first infection. In many cases they do not produce disease; under such circumstances it is termed that this secondary infection does not "take." In numerous other cases, however, lesions are formed, which are termed the lesions of post-primary dissemination.

The fact that all of the tissues of the body have become allergic because of the first infection, tends to produce a local reaction wherever these disseminated bacilli may lodge, which tends to localize these lesions. This allergic reaction is a specific one and belongs to the group of reactions which are included under the general term of immunity reactions, but does not produce immunity in the sense of protection against reinfection.

In addition to this allergic change each individual has his or her own constitutional reaction to the tubercle bacillus. This constitutional reaction may be one of great susceptibility or of marked resistance, with all intermediate stages; it may be inherited, it may be racial, it may be strictly individual, and in every individual it is subject to considerable variations during his lifetime, depending upon various general factors many of which are little understood but some of which are connected with such generally recognized conditions as intercurrent or debilitating disease, unfavorable social environment, imperfect nutrition and the like.

The effect produced therefore by dissemination of tubercle bacilli may vary greatly according to the dosage and the virulence of the bacilli, but particularly according to the resistance of the tissues at the time, as affected by the specific and constitutional factors above described.

In the great majority of cases the number of bacilli discharged into the blood is small, the reactions are slight, and the lesions and symptoms produced from them are unnoticed. If a large number of bacilli is discharged at one time, we have an acute general miliary tuberculosis.

In other cases we have fairly severe lesions, with symptoms depending upon the severity and the localization of the lesions. These bacilli may, of course, reach any organ of the body, but the lungs are almost universally reached by this dissemination, because of the vast capillary network of the lungs which acts as a screen for any foreign matter passing through the blood stream. When we have local tuberculous lesions in organs of the body which are not accessible to outside infection, such as the bones, kidneys, lymph nodes, etc., we have no escape from the conclusion that they occurred from blood stream dissemination. In the case of the lungs, however, we have usually thought of these post-primary lesions as being due to exogenous reinfection from the inhalation of tubercle bacilli. That they are very frequently not so produced, but rather come from the blood stream dissemination, just as do these other extrapulmonary lesions, is a concept which is now generally accepted, and our problem is, to attempt to recognize these lesions as such, because they differ very materially in behavior from those due to exogenous reinfections, and because this origin of pulmonary

tuberculosis from the blood stream very materially affects our thinking concerning the incidence and dangers of reinfection of the lungs from the outside. It also adds great importance and significance to the presence and character of the original lesions from which these disseminations occur.

The Character and Evolution of Hematogenous Lung Lesions. As a rule, the number of disseminated tubercle bacilli is small, and lodging as they do in the interstitial tissues of the lungs rather than in the walls of the air passages, the symptoms produced are usually systemic at first rather than local. The dose of infection being small, the lesions consequently are small, are productive rather than exudative in character and in general they tend to run a benign course. Coming as they do from infection through the blood stream, these lesions are apt to be bilateral and may lodge in any portion of the lungs, but are particularly prone to persist and develop in the cortical areas of the upper lobes, while they tend to absorb from other parts of the lungs. In the majority of the cases they tend to become fibrotic and calcified and are usually recognized in this form by the roentgenogram when there has been no history of obvious lung disease. As these hematogenous disseminations are apt to occur in crops, we may see the evidence of these successive disseminations in the lungs as lesions of varying size and apparently of varying age. At any time, however, during this process a more acute infection may occur, and even to the point of an acute overwhelming generalized tuberculosis which is particularly apt to occur where the lodgment has been in the walls of the blood or lymph vessels, thus making discharge of large quantities of tubercle bacilli an easy possibility.

As the same blood stream infection may reach any organ of the body, these lung lesions are frequently associated with localized tuberculosis in some other organ, and it may be this extrapulmonary tuberculosis which is first recognized clinically. In the overwhelming majority of such cases, however, this is associated with lung lesions also.

In some cases the hematogenous lesions in the lungs and other organs may develop in a protracted but at the same time progressive manner, less acutely than in the case of acute generalized tuberculosis but at the same time in the course of several months producing a widely disseminated tuberculosis in many organs of the body, resulting in death.

In many more cases, however, the lung lesions with periods of quiescence become intermittently active and tend eventually to involve and to break through into the air passages, especially the smaller bronchi. When this occurs, we have a distinct change in the character and evolution of the disease which then progresses just as though the process had originated in the walls of the bronchi as is the case when the infection is due to the inhalation of bacilli. It is then that pulmonary symptoms such as cough, expectoration, hemoptysis, etc., occur. This form of tuberculosis of the lungs is termed bronchopulmonary phthisis.

Bronchopulmonary Phthisis. In a considerable number of cases bronchopulmonary phthisis is undoubtedly in association with exposure and

exogenous reinfection in an individual who has already become allergic because of his primary infection. A conspicuous example of such lesions is the ordinary infraclavicular infiltration with which we are all familiar and which is usually described under the term adult form of pulmonary tuberculosis. Here again the upper lobe localization is characteristic, but they are apt, at first at least, to be unilateral and they are not apt to be associated with extrapulmonary lesions in organs not accessible to the outside. When well developed, however, there is little to distinguish such exogenous bronchopulmonary phthisis from the endogenous form which we have already considered.

When once established, this localized form of tuberculosis called bronchopulmonary phthisis no longer tends to spread by the blood stream. Such dissemination may occasionally occur, but is rare. The usual extension of this form of tuberculosis is by what is termed intracanalicular spread, that is, by the passage of tubercle bacilli through the normal canals of the body to other organs or to other portions of the same organ. In the case of the lungs this is by the bronchi and is termed bronchogenic spread, and is the usual method of progression of phthisis from the apex downward in the same lung or over into the opposite lung. This spread is often accelerated by favoring circumstances such as hemorrhage. It is by this same route that the larynx becomes infected through the expectoration of sputum, and it is also by the same method of intracanalicular spread that secondary intestinal tuberculosis occurs, due to contact with infected sputum.

When the localized organic tuberculosis is in an organ of the genito-urinary tract, such as the kidney, again spread of the infection occurs through the normal canals downward to the bladder, or if it starts in the epididymis, upward through the genito-urinary canal to the bladder and to the kidney.

This tendency of bronchopulmonary phthisis to extend by this method of intracanalicular spread makes possible the formation of very considerable lesions within a short time and rapid spread of the disease, and changes the general course of the disease when one compares it with the much slower and finer dissemination of infection which occurs through the hematogenous route.

In general, in every case of tuberculosis, whether it has developed hematogenously or intracanalicularly, the course of the disease is apt to be intermittent, with periods of exacerbation and remission, which correspond to these recurrent discharges of infection.

The course also varies with the amount of such discharge, with the constitutional resistance and the specific allergy of the tissues, both of which vary in different individuals and in the same individual at different times, and also is influenced by certain accidental factors such as the occurrence of hemorrhage or the discharge of large quantities of tubercle bacilli at one time, either into the blood stream in the case of hematogenous dissemination or into the bronchi in the case of bronchogenic dissemination.

An important fact to recognize is that the clinical manifestations of tuberculosis are practically invariably those of a secondary infection, and that consequently primary infection does not afford a true degree of protection, certainly nothing that we can call a true acquired immunity. It is also important to bear in mind that once there is a primary tuberculous focus in the lymph nodes or in any other organ of the body, the absolute healing of such lesions is a matter of great uncertainty, and that consequently the old dictum, "once tuberculous, always tuberculous," is near to the truth, and inasmuch as these slight lesions from which hematogenous forms of tuberculosis arise are so small and so often give no symptoms, the hazards which attend their existence should be more thoroughly recognized, and if a considerable proportion of disabling or fatal phthisis arises from this source then the measures which may be taken to prevent the occurrence of such active disease from them should be thoroughly understood.

Clinical Forms of Hematogenous Pulmonary Tuberculosis

Diagnosis. The recognition of the hematogenous origin of acute general miliary tuberculosis and of the disseminated protracted progressive forms of the disease, is easy. At the other end of the scale, after bronchopulmonary phthisis has occurred the decision as to whether this occurred from the hematogenous or the exogenous route is extremely difficult, if not indeed impossible.

In other cases the association of a definite type of pulmonary lesion recognized during life, with an extrapulmonary tuberculosis may lead to the inference that both lesions are from the same hematogenous source.

In certain other cases the occurrence of these localized lung lesions, even though apparently healed as they may appear with the roentgen-ray, associated with recurrent mild systemic disturbances of general health, such as chronic poor nutrition, irregular slight rises of temperature, digestive disturbances, undue malaise and fatiguability, may lead to the suspicion of a tuberculous infection mild in degree and possibly hematogenous in source as the cause of such symptoms.

In the lungs, these hematogenous lesions at first not being open to the air passages, may produce no pulmonary symptoms whatever. In other cases the first chest manifestation may be an acute pleural effusion, which is probably very frequently of hematogenous origin. In other cases a small calcified nodule may ulcerate a small vessel, causing a slight hemoptysis. Careful study of the roentgenological evidences of tuberculosis will show that these interstitial lung lesions before bronchopulmonary phthisis has developed have a fairly characteristic appearance. They are usually small and multiple and usually bilateral, with a definite tendency to localization in the upper lobes and to marked calcification. In other cases there are very numerous granular densities throughout the lung fields, closely simulating the appearance of a general miliary tuberculosis, but without

any of the acute systemic symptoms of this disease. Such miliary lesions often come in crops, frequently disappear in a period of a few weeks or months, and may reappear at varying intervals, associated with a varying degree of constitutional disturbance, often very slight.

In still other cases there is a tendency for the infection to travel from the interstitial tissues of the lungs along the lymphatics, giving a strand-like roentgen-ray appearance which has been likened to the meshes of a veil. In other cases the lodgment of the tubercle bacilli may cause rapid caseation, with the formation of small cavities with the characteristic punched-out appearance, very thin walls and surrounded by apparently normal tissue, quite different from the appearance of the ordinary cavity of fibrocaseating phthisis. Such cavities often appear and disappear very rapidly, changing their shape easily, and sometimes may develop into ordinary bronchopulmonary phthisis.

The recognition of these clinical forms of so-called hematogenous pulmonary tuberculosis is largely attained by skilful study of the roentgenogram. Naturally, this leaves such interpretation open to differences of opinion and has led to a very considerable discussion as to the actual scientific basis upon which the diagnosis of these hematogenous forms rests. But, in general, as one comes to study these cases and thinks of them in terms of a lack of local symptoms in the early stages and the frequent association with tuberculous lesions in other parts of the body of undoubtedly hematogenous origin, one gets gradually to recognize a group of pulmonary cases which one believes to be of hematogenous origin.

Moreover, frequently in these cases the roentgen-ray will definitely show the remains of the primary complex both in the lungs and particularly in the tracheobronchial lymph nodes, and in the case of the latter often associated with large densities with more or less calcified deposits, but also showing the possibility of caseating lesions still existent.

Classification. Our review of the pathological and clinical manifestations of tuberculosis will now enable us to consider a question raised earlier, namely, the problem of classification.

We have seen that the ordinary disabling pulmonary tuberculosis is bronchopulmonary phthisis, and everybody realizes that this is due to a reinfection, whether this be exogenous or endogenous, and also everybody realizes that this form of phthisis is much more common in young adult life than it is among children. On the other hand, it appears obvious that there is at least a strong probability that many cases of bronchopulmonary phthisis owe their origin to previous lesions which have been disseminated from the primary infection which occurred in childhood, and that in such cases at least the development of the bronchopulmonary phthisis in adult life should be correlated with the earlier manifestations of the same disease. It is also important to remember that the so-called adult type of phthisis really occurs quite frequently in childhood.

But even more important is it to remember that the childhood type of tuberculosis is recognizable in a very large number of adult individuals who have not as yet at least developed bronchopulmonary phthisis, and that also not infrequently in adults the forms of disseminated tuberculosis which we recognize as more common in children, may occur.

The question is therefore raised as to whether it is desirable to bring in the question of age distribution in any system of classification, and whether it would not be more helpful to the understanding of the problems involved if we thought rather of the underlying pathological processes and pathogenetic principles.

Considering the problem in this way one would rather come to recognize two general clinical forms of pulmonary tuberculosis: (1) The form in which the infection travels by the lymph and blood stream, producing lesions which remain closed in the interstitial structures of various organs of the body. It is recognized that while in this closed form frequently few or no symptoms are exhibited and all that we could recognize is the evidence of old quiescent lesions, on the other hand mild constitutional symptoms do occur in such cases, either because of fresh blood stream disseminations or because of lighting-up of mild activity in preëxisting lesions.

Now, it is in this form of tuberculosis that the lymph nodes are particularly involved, and that as far as the lungs are concerned there are very few if any focal symptoms; and it is this form which is often associated with lesions in extrapulmonary organs.

While this is the usual form of tuberculosis seen in childhood, it must be remembered that the lesions in either a quiescent or an obsolete state persist throughout life and can be recognized, so that careful examination of many adults who have no symptoms will definitely demonstrate the presence of this so-called childhood form of tuberculosis.

Bard [13] and Piéry [14] devised a very detailed classification of the pulmonary forms of this type of tuberculosis, and Neumann [29] has adopted and amplified this classification for clinical use into a very complex system. While the various forms which these authors describe can be recognized after careful study, their very complexity makes them cumbersome and detracts from the usefulness of such classification.*

I have found it simpler and more practicable to include all of these forms under the general designation of lymphohematogenous tuberculosis, while recognizing the fact that this type of the disease develops many various phases during its evolution.

(2) In very strong contrast to this type of tuberculosis we have the bronchopulmonary phthisis. Here, we have serious, often disabling or fatal disease with usually definite pulmonary symptoms and with spread of the disease not by the blood stream but through the canal system of the body, particularly in the case of the lungs through the bronchi. This type

* I have described the main forms included in this classification in a previous communication (Am. Rev. Tuberc., May, 1934).

of disease, as already stated, may occur in childhood but usually does not develop until young adult life. But inasmuch as we have already seen that the recognizable childhood types persist into adult life, the question which arises is: Is the bronchopulmonary phthisis due to an entirely new infection from the outside, or is it due to a flaring-up of these old long-standing childhood lesions? If, as it seems to be true, it often may be due to such lighting-up of childhood lesions, the disease is therefore a continuous one and should be thought of rather in terms of whether the infection is confined in the closed tissues of the body or whether it has gained access to the external mucous membrane surfaces of the bronchi. It is the latter condition which converts it into a serious, disabling disease.

It is a very important and interesting problem not yet solved as to why such latent tuberculosis does not develop more frequently into open phthisis during childhood, and more important still as to why in some cases in adults it so develops into open phthisis and in so many other cases it does not. The correct solution of this problem would undoubtedly lead to the prevention of many cases of pulmonary phthisis which now occur.

The National Tuberculosis Association classification of pulmonary tuberculosis applies in the main to the various stages of this form of tuberculosis, namely, bronchopulmonary phthisis. What we are designating as lymphohematogenous tuberculosis is classified in the American system as the childhood type of pulmonary tuberculosis.

While the National Association classification has a wide field of usefulness, it has the disadvantage of all fixed systems in that it lacks flexibility and encourages the concept of pulmonary tuberculosis as a static process. As a matter of fact, the evolution of tuberculosis is a moving or dynamic process subject to frequent change. The minimal case of today, for example, may be a III C case tomorrow, following a hemorrhage with widespread bronchogenic dissemination of new lesions and with marked constitutional disturbances.

Without discarding the use of this classification entirely, I have found the less static division of cases into: (a) the lymphohematogenous type with closed interstitial lesions and extension through the lymph and blood stream, and (b) the bronchopulmonary phthisis type, with extension through the air passages, most helpful in the understanding of the various phases of this kaleidoscopic disease. I believe that the classification into childhood and adult types may be actually misleading.

Prognosis. It is obvious from our discussion of the clinical course of these cases of hematogenous tuberculosis that the prognosis in any individual case will depend upon many factors and would be very variable. The important thing would appear to be to recognize the fact that we are dealing with the form of tuberculosis which while it remains in this closed form is apt to run a benign course, with very few constitutional symptoms which usually respond satisfactorily and promptly to rest treatment.

On the other hand, it is important to realize that many of these cases have no symptoms at all during life, but in some of these apparently well people reactivation of their lesions will occur and disabling phthisis result. Once recognized, therefore, this form of tuberculosis should never be entirely dismissed as a negligible condition.

After these pulmonary lesions have gone over into bronchopulmonary phthisis, which as we have seen they frequently do, the prognosis in such cases presents all of the variations and possible seriousness which is well recognized in this form of the disease. Most frequently it is the determination of whether we are dealing with the closed lymphohematogenous form, or the open bronchopulmonary form, that is important from the standpoint of prognosis and of treatment.

Treatment. As long as these hematogenous lung lesions remain localized and in the quiescent stage they may need little or no treatment, but the danger of exacerbation being what it is, their recognition calls for the institution of a program of repeated examination and supervision to provide a protective environment which would prevent them from becoming active disease and which also may have the effect of preventing further disseminations of bacilli from the original focus.

The physician recognizing such cases would not put them in a sanatorium, but would have them report regularly for check-up of the general condition and particularly for repeated roentgenological examination. Every effort should be made to keep the state of nutrition of such a patient good, to avoid over-exertion and stress of every sort.

We are all familiar with the results of such a program for children who have tuberculous tracheobronchial lymph nodes and who respond positively to the tuberculin test. They need more rest than the normal child; they are restricted as to hard exercise; they are given more out-of-door life; special attention is given to their diet and the improvement of their nutrition, with the addition of vitamins, particularly of vitamin D in the form of cod liver oil or some of its derivatives. It is in a similar way that artificial or natural heliotherapy may exert beneficial effects in such cases.

What we now have to recognize is that this type of disease is not confined to children, that the danger of development of hematogenous forms lasts into adult life, that the safeguard and the protection which we well recognize is useful for certain children, is equally important for many adults. If cases of this sort are recognized as possible sources of active tuberculosis, there can be no doubt that many of the advanced forms of the disease, including many cases of progressive bronchopulmonary phthisis, could be prevented.

According to our modern ideas, the treatment of bronchopulmonary phthisis after it occurs, whether from endogenous or exogenous reinfection, is the prevention of bronchogenic spread, particularly after caseation and cavity formation have occurred, and this bronchogenic spread we now know can be most satisfactorily and quickly prevented by bed rest aided by suitable

mechanical means, in which term we include the various types of collapse therapy such as artificial pneumothorax and some of the more radical forms of surgical treatment.

In general, this form of mechanical treatment is not applicable to the usual forms of hematogenous pulmonary tuberculosis before they have gone over into the stage of bronchopulmonary phthisis.

The slow evolution which occurs in many forms of hematogenous tuberculosis of the lungs suggests that it is in this form of the disease that possibly changes in tissue reaction might be artificially produced by some form of specific therapy. This is not by any means a generally accepted idea, but the fact that even the rather generally discredited tuberculin treatment still does appear in certain types of cases to have beneficial results, and that it is still widely used in such definitely hematogenous forms of the disease as occur in the eye or to a less extent in the lymph nodes, leads one to raise the question whether if we apply our mechanical methods of treatment to bronchopulmonary phthisis and limit our efforts in experimentation with specific therapy to the hematogenous forms, we may not be able to look forward to the future development of more successful specific therapy. Not a few authorities, of whom Neumann is perhaps an outstanding example, are using tuberculin widely, basing its use on just such principles. The idea at least gives us a basis of some hope for the future.

Prevention. The prevention of disabling lung tuberculosis is in the main the question of the prevention of bronchopulmonary phthisis. This means the prevention of secondary infections; those from the outside may be guarded against by avoiding close association with active sources of infection; those from the inside may be averted by protective measures tending to keep locked-up the infections that already exist, and tending also to keep the general and specific resistance of the individual such that the bacilli which are disseminated do not produce serious forms of the disease.

That this can be done by the program of supervision and protective environment has already been widely demonstrated in the case of children. The extension of this program to similar cases in adults will certainly prevent the development of many cases of progressive tuberculosis which now occur.

The absolute prevention of tuberculosis would appear to depend upon the prevention of the primary infection. That this is not a utopian idea is evidenced by the fact that an increasing number of adults grow up without tuberculous infection, as instanced by the increasing age incidence at which positive tuberculin reactions appear in various groups of the population. The doctrine that the primary infection really protects in some way from tuberculosis must probably be profoundly modified. That this primary infection changes the reaction of the individual to secondary infection is undoubted, but this changed reaction tends toward a more acute form of the disease, and in that sense the individual may die from the effects of his own immunity. This whole problem of the relative protection and relative

danger which lie in the first infection is one of profound scientific and practical interest, which is not by any means completely solved.

Summary

1. The usually recognized clinical form of pulmonary tuberculosis is bronchopulmonary phthisis. This form of the disease is always due to a secondary infection, which may be exogenous, but is very frequently endogenous from the smoldering primary focus or from one of its satellites arising in the form of early or late post-primary hematogenous dissemination.

2. Many other forms of pulmonary tuberculosis recognizable by the roentgenological as well as by the clinical features and course, are due to such hematogenous disseminations. Such processes are usually localized in extent and benign in character, and very frequently the individual with them may go through life with but few symptoms.

3. While many of these processes appear, and may indeed be, for long periods apparently obsolescent, and need then no active treatment, it should yet be remembered that such lesions have potentialities for development, at any time, into serious and fatal forms of the disease. Such cases, therefore, should be regularly examined and the general course of their life regulated and supervised. The development of some sort of specific therapy in the control of this type of lesion is also a possibility of the future.

4. Extrapulmonary tuberculosis—excepting intestinal and laryngeal—is practically always of hematogenous origin, and when recognized should invariably lead to the investigation of the lungs which will very frequently also be found involved in the process.

5. Extension and coalescence of the lesions in pulmonary tuberculosis take place for the most part by intracanalicular spread. Bronchopulmonary phthisis is thus produced, in which mechanical treatment plays its chief rôle. Hematogenous dissemination occurs but infrequently as a complication of manifest bronchopulmonary phthisis. Consequently, such acute forms as miliary tuberculosis are rarely seen in this class of case.

6. The division of pulmonary tuberculosis into two broad types, namely, lymphohematogenous and bronchopulmonary, affords a better conception of the dynamic character of the evolution of the disease than does the rigid adherence to fixed or static systems of classification.

The term childhood type of tuberculosis is misleading for the reason that so often the characteristic evidences of this type persist into adult life when they may develop into more serious forms of the disease.

7. The recognition of the importance of these principles and especially of the rôle of systemic infection, leads us to a better understanding of many forms of tuberculosis, to a more rational method of treatment adapted to each individual case, and to the possibility of preventing many cases from developing from the milder into the more serious forms of the disease.

BIBLIOGRAPHY

1. Cornet, G.: Tuberculosis and acute general miliary tuberculosis, edited with additions by Walter B. James, 1904, W. B. Saunders, Philadelphia.
2. von Behring, E.: Tuberkuloseentstehung, Tuberkulose-Bekämpfung und Säuglingsernährung, Beitr. z. exper. Therap., 1904, viii, 20–52.
3. Petruschky, J.: Tuberkulose und Septicämie, Deutsch. med. Wchnschr., 1893, xix, 317.
4. Hamburger, F.: Allgemeine Pathologie und Diagnostik der Kindertuberkulose, 1910, F. Deuticke, Wien.
5. Albrecht, H.: Über die Tuberkulose des Kindesalters, Wien. klin. Wchnschr., 1909, xxii, 327–334.
6. Ghon, A., Kreider, P., and Kudlich, H.: Zur Entstehung der Reinfektion der menschlichen Lungenphthise, Virchow's Arch. f. path. Anat., 1927, cclxiv, 583–586.
7. Ranke, K.: Primäraffekt, sekundäre und tertiäre Stadien der Lungentuberkulose auf Grund von histologischen Untersuchungen der Lymphknoten der Lungenpforte, Deutsch. Arch. f. klin. Med., 1916, cxix, 297.
8. Marmorek, A.: Beitrag zur Kenntnis der Virulens der Tuberkelbacillen, Berlin. klin. Wchnschr., 1906, xliii, 328.
9. Liebermeister, G.: Studien über Komplikationen der Lungentuberkulose und über die Verbreitung der Tuberkelbazillen in den Organen und im Blut der Phthisiker, Virchow's Arch. f. path. Anat., 1909, cxcvii, 332–384.
10. Löwenstein, E.: Die klinische Bedeutung der Tuberkelbazillämie, München. med. Wchnschr., 1930, lxxvii, 1662–1663.
11. Wilson, G. S.: Tuberculous bacillemia, British Med. Res. Council, 1933, Special Report Series No. 182, London.
12. Landouzy, L.: La typho-bacillose, Second International Tuberculosis Congress held in Washington, September to October 1908.
13. Bard, L.: Formes cliniques de la tuberculose pulmonaire, 1901, Henry Kuendig, Genève.
14. Piéry, M.: La tuberculose pulmonaire, 1910, O. Doin and Fils, Paris.
15. Rist, E., and Doubrow, S.: Les épisodes miliaires évolutifs au cours de la tuberculose pulmonaire chronique, Bull. Acad. de med., 1933, cix, 547–551.
16. Sergent, E.: Les réveils de la tuberculose pulmonaire chez l'adulte, 1933, Masson and Cie, Paris, pages 167–182.
17. Bernard, L.: Les débuts et les arrêts de la tuberculose pulmonaire, 1931, Masson and Cie, Paris, pages 159–193.
18. Bezançon, F., and Braun, P.: Le stade anatomo-clinique précurseur de la phtisie chronique de l'adulte; la tramite tuberculeuse initiale, Presse méd., 1927, xxxv, 1601–1605.
19. Wingfield, R. C.: Chronic pulmonary tuberculosis: a new conception, British Med. Jr., 1933, i, 179–181.
20. Orth, J.: Über tuberkuloese Reinfektionen und ihre Bedeutung für die Entstehung der Lungenschwindsucht, Verhandl. d. Berlin. med. Gesellsch., 1904, Febr. 10.
21. Roemer, P. H.: Weitere Versuche über Immunität gegen Tuberkulose durch Tuberkulose. Zugleich ein Beitrag zur Phthisiogenese, Beitr. z. Klin. d. Tuberk., 1909, xiii, 1.
22. Aschoff, L.: Lectures on pathology, delivered in the United States, 1924, P. B. Hoeber, New York.
23. Redeker, F.: Die neueren klinischen Tuberkuloseanschauungen, 1929, Urban and Schwarzenberg, Berlin and Wien.
24. Loeschcke, H.: Die hämatogenen Tuberkulosen, Beitr. z. Klin. d. Tuberk., 1932, lxxxi, 171–183.
25. Duken, J.: Die klinischen Verlaufsformen der postprimären Lungentuberkulose im Kindesalter, Ergebn. d. inn. Med. u. Kinderh., 1931, xxxix, 344–577.
26. Schürmann, P.: Zur Frage der Gesetzmässigkeiten im Ablauf der Tuberkulose, unter

besonderer Berücksichtigung der Entwicklungsgangslehre Ranke's, Beitr. z. path. Anat. u. z. allg. Path., 1929, lxxxi, 568–657; 1930, lxxxi, 551–640.

27. PAGEL, W.: Pathologische Anatomie der hämatogenen Streuungstuberkulose, Ergebn. d. ges. Tuberk., 1933, v, 231–350.

28. RÜDEL, H.: Die Verteilung der Grundformen der Tuberkulose auf das Sektionsmaterial des Heidelberger Pathologischen Instituts, Beitr. z. Klin. d. Tuberk., 1931, lxxviii, 243–249.

29. NEUMANN, W.: Die Klinik der beginnenden Tuberkulose Erwachsener, 1923, Rikolo Verlag, Leipzig and Wien.

THE BLOOD SEDIMENTATION TEST: ITS USE AS A ROUTINE, ESPECIALLY IN PULMONARY TUBERCULOSIS *

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IN 1918 Fåhraeus [1] first noted an increase in the sedimentation rate of red cells in citrated blood in pregnant women. At once this was hailed as a new test for pregnancy; but it was soon found to be unreliable in the early months when, of course, its importance was greatest. The test is reliable for pregnancy after the twelfth week if no concurrent infection exists, but by that time its diagnostic value has necessarily been lost. Furthermore, it was soon discovered that acute and chronic infectious processes and malignant new growths had a marked effect upon the sedimentation rate.

TECHNIC EMPLOYED

In this work the technic of Cutler [2] has been used. In brief it is as follows: " Specially designed sedimentation tubes of 1 c.c. capacity are used, graduated into 50 mm. divisions, with 0 at the 1 c.c. level, each millimeter indicating 0.02 of 1 c.c. One-tenth of 1 c.c. of a 3 per cent sodium citrate solution and 0.9 c.c. of blood, obtained by puncture of a suitable vein, are gently mixed in a 2 c.c. syringe and poured into the sedimentation tube. The position of the sedimenting column of erythrocytes is determined every five minutes for an hour. The observations are recorded on charts that have been designed for the purpose, on which the horizontal lines represent the divisions on the tube and the vertical lines the intervals of time. Graphs are then constructed, which not only show the position of the sedimenting column of erythrocytes at any period of time during the first hour, but also portray the changes in velocity that occur during the process of sedimentation."

Walton [3] feels that the sedimentation rate should be corrected to correspond to a standard of 5,000,000 red cells to the cubic millimeter as he finds that the rate is markedly increased in proportion to the degree of anemia present. He cites as an example the rate in a normal individual whose blood was diluted to represent respectively blood containing four, three, two and one million red cells to the cubic millimeter. His table reads as follows:

Normal Individual

5 Tubes	*Rate in One Hour*
5 million R.B.C.	1. mm.
4 " "	6. "
3 " "	10.5 "
2 " "	20. "
1 " "	27.5 "

* Read at the Chicago meeting of the American College of Physicians, April 18, 1934.

This method, from the standpoint of scientific accuracy, is probably the ideal one to use. As a practical clinical procedure, however, it is intricate and time-consuming, while that of Cutler is simple and rapid. Furthermore if, as in all my cases, red counts are made at the same time that the sedimentation rate is estimated, allowance can be made for the various degrees of anemia encountered. The procedure now under consideration is a practical office, bed-side or dispensary test that can be done with a minimum of effort, and in which the human equation does not figure in reading the result.

Again, though the most important methods now are those described by Fåhraeus,[1] Linzenmeier,[4] Gram,[5] Rourke and Ernstene,[6] and Cutler,[2] only Gram, and Rourke and Ernstene (besides Walton [3]) make any attempt to correct the sedimentation rate for fluctuations in red cell count. This should be fairly good evidence that the majority of workers have found the method here employed clinically satisfactory and trustworthy.

Nature of the Reaction

No definite proof of the cause of increased sedimentation rate has been brought forth, but it is being generally accepted that the phenomenon depends upon the amount of cellular destruction going on in the body. In the ordinary wear and tear of life there is constantly present a process of tissue destruction accompanied by a similar amount of tissue repair. To quote Cutler [2]: "Should the amount of tissue destruction pass beyond the normal, then the stability of the blood is seriously disturbed and the red blood cells settle out quickly from the plasma. . . . Regardless of the disease present, whether it be active pulmonary tuberculosis, malignancy, pelvic inflammatory disease, and acute infections such as typhoid fever, or any disease in which tissue destruction is going on at a greater pace than normal, the rapidity of settling of the red blood cells is in direct proportion to the severity of the disease."

Bortree [7] says that: "Various theories have been propounded to explain the alteration in the rate of sedimentation: changes in electrical potential of the cells, alteration of cell volume or mass, viscosity or chemical variance, etc. Present opinion is that the relative speed of sedimentation of erythrocytes is dependent upon the colloidal chemistry of the blood, and chiefly upon the globulin-fibrinogen ratio. In conditions involving rapid destruction of tissue, there is found in the blood an excess of fibrinogen. In any case where the content of fibrinogen in the blood is above normal, the speed of sedimentation is increased. The greater the increase of fibrinogen content, the more rapid the sedimentation rate, so that the two curves run virtually parallel. However, the sedimentation test is so much simpler than a fibrinogen determination that it is to be preferred in clinical work."

Limitations of Sedimentation Test

The test is absolutely non-specific. It is an index of activity of infection or of malignant growth. It is, however, a valuable and useful prognostic aid and in this connection has been used more particularly in gynecology and in tuberculosis. At times it will act as a "lead," as when a patient is seen with practically negative physical and laboratory examinations but with a high sedimentation rate. One can then be sure that there is some process (other than pregnancy) causing active cellular destruction, and search for the offending cause must be continued. Practically all acute infections are accompanied by an increase in the sedimentation rate, but there is no relationship between the temperature curve and the sedimentation curve, nor is there any relationship between the degree of leukocytosis and the rapidity of sedimentation. (Chart 1.)

Chart I

Diseases Grouped According to Sedimentation Rates (Cutler)

With an Abnormal Sedimentation Rate

1. Chronic infectious diseases, such as tuberculosis and syphilis.
2. Acute infectious diseases, such as pneumonia, septicemia, acute endocarditis, the exanthemata and acute bronchitis.
3. Malignancy.
4. Localized suppurations, such as pelvic inflammatory disease, suppurative mastoiditis, suppurative sinusitis, empyema of the gall-bladder, bronchiectasis.
5. Acute intoxication, such as lead and arsenic poisoning.
6. Certain endocrine disturbances, such as thyroid toxicosis.

Influencing the Sedimentation Rate Very Little If At All

1. Simple catarrhal inflammations, such as acute catarrhal appendicitis, simple rhinitis and colitis.
2. Chronic ulcerations of small extent, such as gastric or duodenal ulcer.

Not Influencing the Sedimentation Rate

1. Functional diseases, such as the various neuroses, and neurasthenia.
2. Certain nervous diseases, such as dementia precox.
3. Focal infections, such as abscessed teeth, diseased tonsils and chronic sinusitis.
4. Metabolic diseases, such as uncomplicated diabetes and essential hypertension.
5. Allergic diseases, such as asthma and hay fever.
6. Most skin diseases.
7. Simple growths, such as fibroma, lipoma and fibromyoma.
8. Simple cysts.
9. Chronic valvular disease of the heart.

It is generally conceded that in tuberculosis the sedimentation test represents the intensity and degree of activity of the process. Walton [3] states that "a normal sedimentation rate has never been found with an *active* tuberculous focus." I cannot agree with this statement, but of course the same definition of "activity" must be employed. The one that I prefer is: "Activity is present when the patient is suffering from symptoms, which symptoms are due to tuberculosis." Adopting that as a standard, I have seen many individuals with a normal sedimentation rate who had unquestionable evidences of activity.

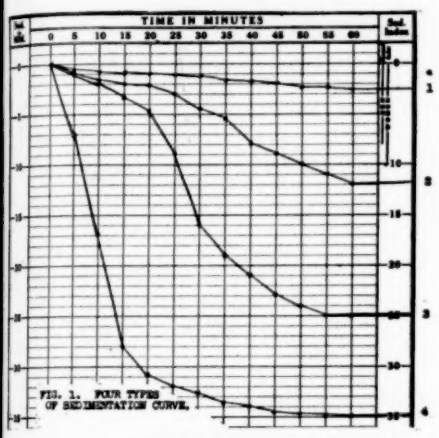

FIG. 1. FOUR TYPES OF SEDIMENTATION CURVE.

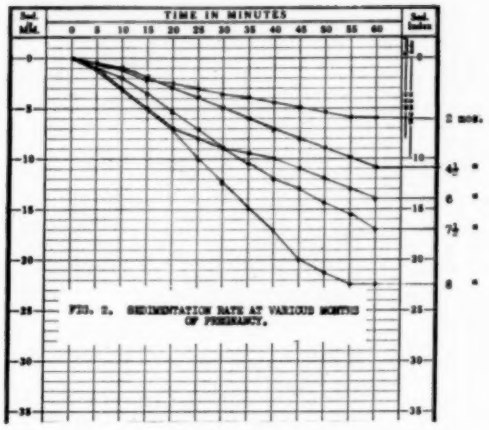

FIG. 2. SEDIMENTATION RATE AT VARIOUS MONTHS OF PREGNANCY.

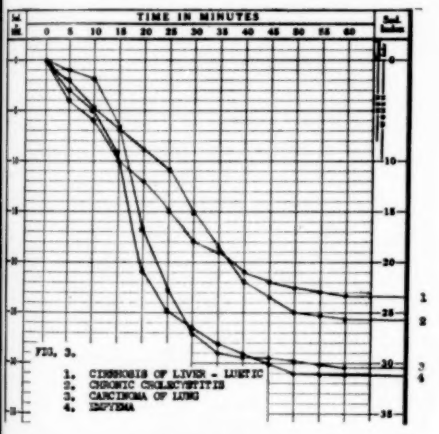

FIG. 3.
1. CIRRHOSIS OF LIVER - LUETIC
2. CHRONIC CHOLECYSTITIS
3. CARCINOMA OF LUNG
4. ERYTHEMA

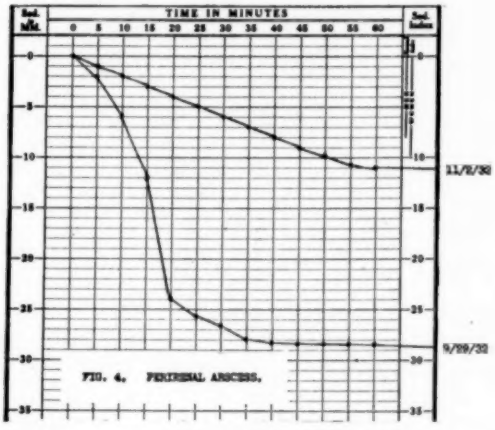

FIG. 4. PERIRENAL ABSCESS.

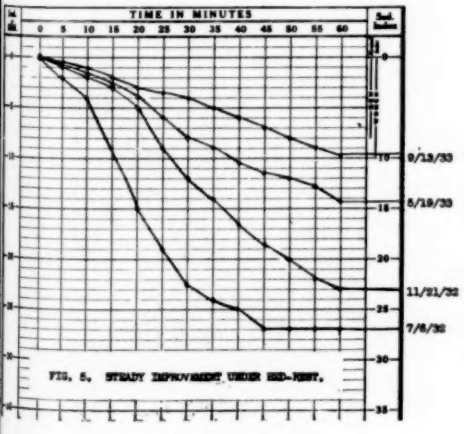

FIG. 5. STEADY IMPROVEMENT UNDER REST.

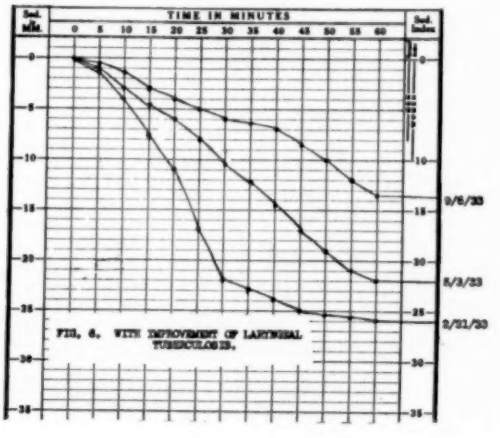

FIG. 6. WITH IMPROVEMENT OF LARYNGEAL TUBERCULOSIS.

It is true that in tuberculosis the sedimentation rate is an excellent guide to progress and most closely parallels radiological changes. If the roentgen-ray findings are equivocal, as they so often are, the nature of the sedimentation test will often determine the direction in which the patient is headed. Roche [8] uses the sedimentation rate as an index for the beginning of exercise and even in the presence of normal pulse and temperature rates waits until the sedimentation rate is approaching normal before allowing exercise. Again, if a patient is simply not " feeling fit " and yet presents no objective symptoms, a normal sedimentation rate would point toward a nervous etiology rather than an organic one. A rise in the sedimentation rate may precede hemoptysis. Repeated tests are very valuable as the rate will change rapidly for better or for worse. From an economic standpoint, the ease and practical costlessness of the test add to its value.

The sedimentation test is not a substitute for any existing clinical or laboratory procedure but is complementary to them. The test is not infallible, but neither are the majority of laboratory procedures. Very rarely, in less than 1 per cent, a normal rate will be found in the presence of active clinical disease, save in certain cases of tuberculosis as mentioned above.

Types of Graphs (Figure 1):

All authorities recognize four distinct types of graph:

1. A horizontal or practically horizontal line,
2. A diagonal line,
3. A diagonal curve,
4. A vertical curve.

The nearer the line is to horizontal the more normal it is, but thousands of observations have fixed the high normal limit at 8 mm. in men and 10 mm. in women.

Figure 2 shows the nature of the curves at various months of pregnancy. I was able to obtain these through the courtesy of my colleague, Dr. R. A. White, of Asheville.

Figure 3 shows the curves in four widely different conditions coming under my observation; namely,

Cirrhosis of liver—luetic
Chronic cholecystitis
Carcinoma of lung
Empyema—non-tuberculous

Figure 4 is that of a patient who had been wrongly diagnosed as a case of acute fibrinous pleurisy. The clinical picture was not that of pleurisy and the high sedimentation rate pointed to something else. In a few days a perirenal abscess was discovered, evacuated surgically, and recovery set in. The sedimentation rate rose shortly to within practically normal limits.

My work on the sedimentation test in tuberculosis is based on 272

patients, in whom a total of 552 sedimentation rates were made by my technician, Miss Mary Roach; 204 of these patients had diagnosticable tuberculosis; of the remaining 68, there were 51 that were diagnosed as having no definite disease, many of these having requested examination because of relationship to or contact with tuberculous patients. The remaining 17 patients had conditions which are not of sufficient importance to be enumerated in detail in this communication, though certain outstanding ones are mentioned.

Of the 204 having tuberculosis, there were 44, or 21 per cent, in stage 1; 54, or 27 per cent, in stage 2; and 106, or 52 per cent, in stage 3; the classification being that adopted by the National Tuberculosis Association and corresponding to minimal, moderately advanced and far advanced, respectively.

Due perhaps to an innate dislike for long and complicated tables, I have felt that it would be most instructive to cite various typical cases showing the reliability of the sedimentation test as a corroborative and occasionally as a warning factor as to the progress of patients suffering from tuberculosis.

Figure 5 shows the sedimentation rates in a man with a far advanced bilateral tuberculosis in whom any type of pulmonary compression was out of the question because of the anatomical distribution of the lesions. Fifteen months of bed-rest brought about quiescence of the pathological process and corresponding slowing in the sedimentation rate.

Figure 6 shows the improvement in the sedimentation rate in a patient with advanced but stationary lung disease, but with a severe laryngeal tuberculosis. Under treatment by the actual cautery at the hands of Dr. J. B. Greene, of Asheville, marked improvement took place in the laryngeal condition which was faithfully reflected in the change in the sedimentation rate.

Figure 7 is from the records of a most remarkable case: a patient with marked bilateral pulmonary involvement who did badly for three months; a pleural effusion developed on the left side (that of major involvement) and immediately marked clinical improvement set in, which is apparent from the slowing in the sedimentation rate.

The next two cases are in what I term the " warning " class. Figure 8 shows the rate in a patient with minimal physical and radiological signs of disease and clinically symptom-free. The roentgen-ray and physical signs remaining stationary for several months, she was allowed to return to her home in Washington classified as " apparently arrested," despite the fact that the sedimentation rate had remained practically stationary. Within one week of her return she had a profuse hemoptysis which was repeated within three weeks, and resort was had to artificial pneumothorax, as a result of which she is now doing satisfactorily. I believe I was guilty of an error of judgment in allowing the girl to discontinue her cure in the absence of a normal sedimentation rate, though I believe she would have had her hemoptysis just as promptly in Asheville as in Washington.

Figure 9 is that of a patient still under treatment, with an advanced lesion of the left lung with cavity formation. Pneumothorax was successfully induced, but adhesions prevented the closure of a four centimeter cavity. Internal pneumolysis was then successfully attempted by Dr. Julian Moore and the cavity was reduced to two centimeters in diameter. This patient is in excellent clinical condition; well up in weight, fever-free, coughing and expectorating far less than before her pneumolysis; but the persistently high sedimentation rate is ominous and I fear that she is headed either for a hemorrhage from the as yet unclosed cavity or, more probably, for a spread of disease in the contralateral lung, which unfortunately is not free of involvement. Time alone will tell the tale, but the sedimentation rate in this patient has caused me to handle her most carefully.

The next four cases illustrate improvement noted in patients subjected to various forms of pulmonary compression.

Figure 10 shows the marked slowing in the sedimentation rate after five weeks of treatment by artificial pneumothorax. The patient, a slip of a girl, had a very active, wholly unilateral process. The results following compression were clinically startling: prompt disappearance of fever, practically total suppression of cough and sputum and corresponding physical betterment. The slowing in the sedimentation rate is certainly striking.

Figure 11 illustrates betterment as evidenced by the sedimentation rate in a patient with an apical cavity in whom artificial pneumothorax could not be induced because of adhesions. A phrenic neurectomy was done by Dr. Julian Moore, rendering the patient symptom-free and showing within a month marked slowing in the sedimentation rate.

Figure 12 is from the records of a patient with unilateral cavitation who, after several months of bed-rest with no improvement, was given artificial pneumothorax; but, as so often happens, the cavity was held open by adhesions. An internal pneumolysis was successfully done, again by Dr. Moore. Clinical improvement was gradual but steady, as is shown by the four sedimentation rate estimations between February and October, 1933. While the patient still has a pleural effusion, he is clinically well and wholly symptom-free.

Figure 13 shows the rapid improvement in a patient with a far advanced fibro-caseous tuberculosis of one lung. She was definitely on the downgrade when a three-stage paravertebral extrapleural thoracoplasty was begun by Dr. W. P. Herbert about July 15, 1933. Remarkable clinical improvement was brought about, improvement which is borne out by the marked slowing of her sedimentation rate. It must be remembered that within practically four weeks this patient was subjected to three major operations which greatly exhausted her physical resources.

Figure 14 is an interesting one. The patient had a unilateral cavity for which artificial pneumothorax was successfully instituted. Mechanically the procedure was a success. The cavity was closed but the patient did not do well. No spread of disease could be found in the contralateral lung.

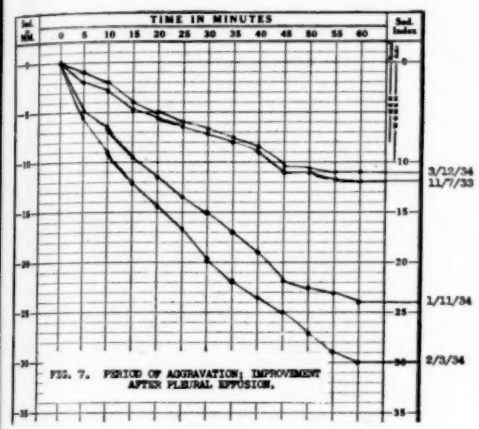

FIG. 7. PERIOD OF AGGRAVATION; IMPROVEMENT AFTER PLEURAL EFFUSION.

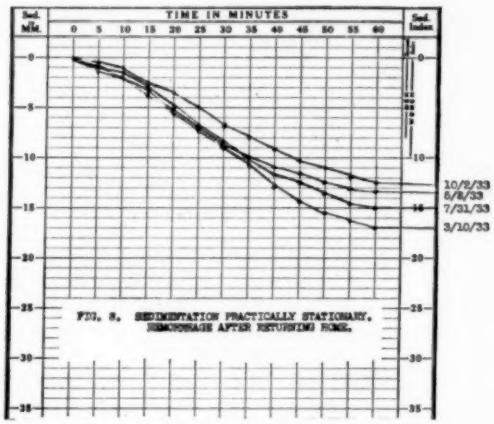

FIG. 8. SEDIMENTATION PRACTICALLY STATIONARY. HEMOPTOSIS AFTER RETURNING HOME.

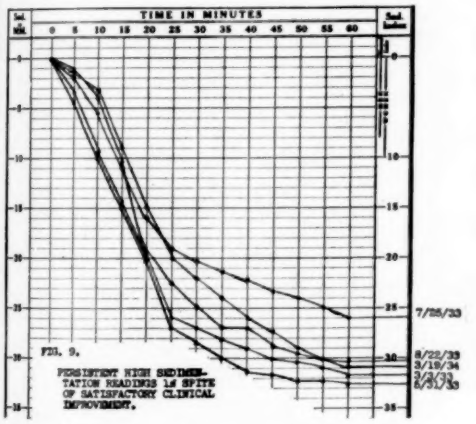

FIG. 9. PERSISTENT HIGH SEDIMENTATION READINGS IN SPITE OF SATISFACTORY CLINICAL IMPROVEMENT.

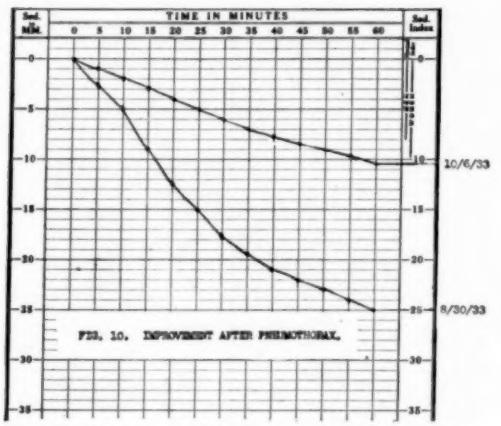

FIG. 10. IMPROVEMENT AFTER PNEUMOTHORAX.

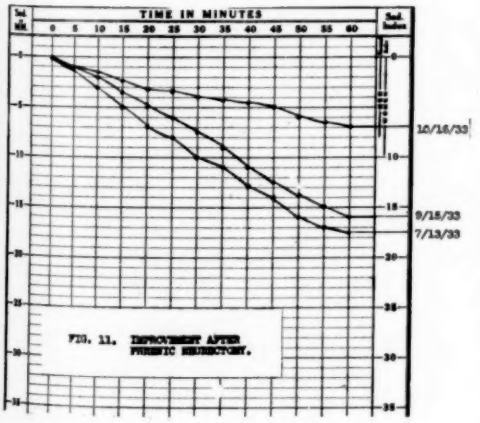

FIG. 11. IMPROVEMENT AFTER PHRENIC NEURECTOMY.

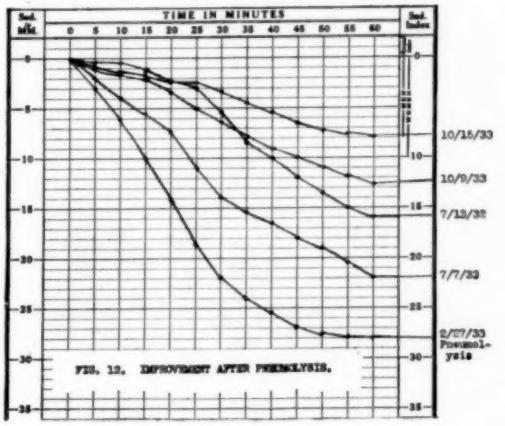

FIG. 12. IMPROVEMENT AFTER PHRENOLYSIS.

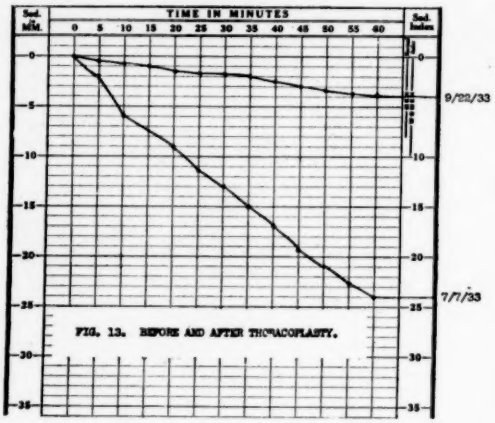

FIG. 13. BEFORE AND AFTER THORACOPLASTY.

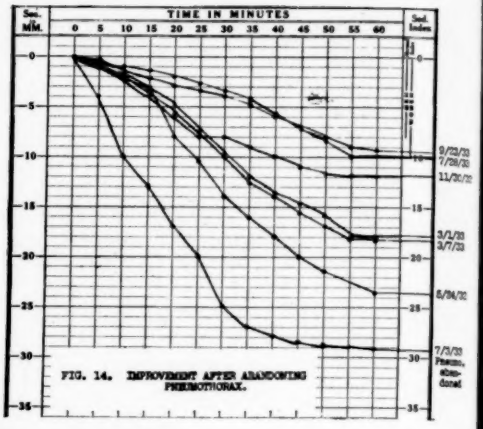

FIG. 14. IMPROVEMENT AFTER ABANDONING PNEUMOTHORAX.

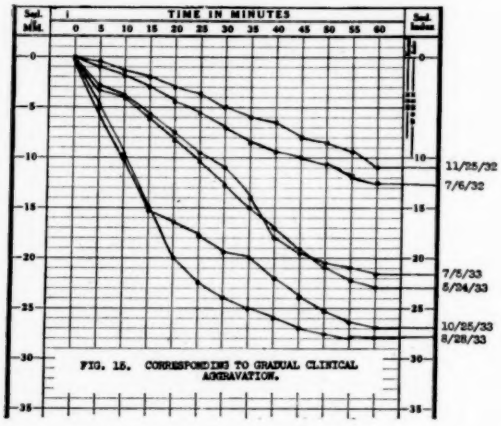

FIG. 15. CORRESPONDING TO GRADUAL CLINICAL AGGRAVATION.

Digestion was bad, anorexia ensued, loss of weight resulted and her last state was worse than her first. On July 3, 1933, pneumothorax was abandoned, the air remaining in the pleural cavity aspirated in an effort toward aiding the compressed lung rapidly to reëxpand. The patient literally took on a new lease of life. Note the marked change in the sedimentation rate between July 3 and July 28, 1933.

Figure 15 well illustrates the changes in a patient gradually but steadily going downhill over a period of almost 16 months despite the induction of an artificial pneumothorax and the performance of a phrenic neurectomy. This patient has never had enough resistance to go " over the top," a fact which the sedimentation rate emphasizes.

As a result of two years' experience with this test and because of the results obtained as evidenced by the charts shown here, I feel that it is one of real value. I agree with Townsend [9] that it parallels the severity of the disease. Banyai [10] believes that no tuberculous patient should be discharged until the rate is normal. I am rather in agreement with him, having in mind the girl whose graphs I have shown and who had a hemoptysis within a

week after her return home. From all clinical evidence, this girl should have had a normal sedimentation rate, yet she could never quite obtain one. Walton [3] has such an excellent paragraph on the value of the test that so exactly reflects my own conclusions that I cannot refrain from quoting him:

> It is a most delicate and sensitive reaction, which reflects very faithfully the state of equilibrium of the blood in relation to any pathological process. It is not specific for any disease; therefore, its uses as a specific diagnostic agent are almost limited to the domain of tuberculosis, where it may be employed in conjunction with a small provocative dose of tuberculin. Used cautiously, however, and as an adjunct to the clinical picture, the sedimentation test, if correctly interpreted, will be found to possess great value, and will often weigh down the scales of differential diagnosis.

In my own experience, based mainly upon cases of pulmonary tuberculosis, I have come to rely greatly upon it, feeling that it reënforces physical, radiological and symptomatic evidence, and frequently presages oncoming evil, or, on the other hand, gives one confidence in the ultimate outcome when clouds loom dark on the clinical horizon.

BIBLIOGRAPHY

1. Fåhraeus, R.: The suspension-stability of the blood, Acta med. scandinav., 1921, lv, 1–228.
2. Cutler, J.: Finger puncture method for blood sedimentation test, Am. Jr. Med. Sci., 1927, clxxiii, 687–694.
3. Walton, A. C. R.: Erythrocyte sedimentation test; clinical and experimental study, Quart. Jr. Med., 1933, ii, 79–115.
4. Linzenmeier, G.: Untersuchungen über die Senkungsgeschwindigkeit der roten Blutkörperchen, Pflüger's Arch. f. d. ges. Physiol., 1920, clxxxi, 169.
5. Gram, H.: Über die Correction der Senkungsreaktion für den Einfluss des Zellvolumenprocentes (Haemoglobin) und über die normalen Grenzen der Senkungsreaktion, Acta. med. scandinav., 1928, lxviii, 108–122.
6. Rourke, M. D., and Ernstene, A. C.: Method for correcting erythrocyte sedimentation rate for variations in cell volume percentage of blood, Jr. Clin. Invest., 1930, viii, 545–559.
7. Bortree, W. L.: Blood sedimentation as a prognostic aid, Trans. Am. Climat. and Clin. Assoc., 1932, 41.
8. Roche, H.: Blood sedimentation rate in pulmonary tuberculosis; its value in management of patient, Brit. Med. Jr., 1932, i, 466–468.
9. Townsend, D., and Rogers, H. M.: A contribution to the study of the erythrocyte sedimentation reaction, Jr. Lab. and Clin. Med., 1928, xiii, 819–827.
10. Banyai, A. L., and Anderson, S. V.: Erythrocyte sedimentation test in tuberculosis, Arch. Int. Med., 1930, xlvi, 787. Quoted by Bortree.[7]

THE SURGICAL TREATMENT OF PULMONARY TUBERCULOSIS *

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AN analysis of our present knowledge of the advances made in the treatment of pulmonary tuberculosis clearly indicates that rest is the foundation and its development the only important and successful remedial furtherance in the treatment of this disease. Detweiler is credited with being the first to advocate rest as a therapeutic measure; but Joseph H. Pratt points out that Trudeau indorsed it before Detweiler. From a surgical standpoint, the development of rest as a curative method forms the basis of modern phthisiotherapy.

Valuable adjuncts to bed rest are postural rest on the diseased hemithorax and shot-bags placed on the front of the chest when the patient lies in the dorsal position. It is true that these expedients prove sufficient to bring about a recovery in many cases of pulmonary tuberculosis in the early, and even in the moderately advanced, stages. However, if cavities have already formed, the rest regimen is too often a failure because of the frequency of bronchogenic extension of disease to the same and opposite lung, the larynx and gastrointestinal tract.

The importance of closing cavities promptly is gradually being recognized, and valuable time is not wasted so grievously on prolonged sanatorium routine while other vital means could be utilized. The ever present possibility of disease extension is not the only danger to be regarded, for there is also the additional menace to the health of others. We have for an illustration the ambulant cavity case who looks and feels well, except for cough and expectoration. It is self-evident that the sooner the cavity is closed the better—not only for the individual patient, but for those who live and work with him.

The ambulant cavity case as a carrier is strikingly shown by our experience with salesgirls employed in a ladies' specialty shop, where one after the other (numbering six) developed tuberculosis. The source of infection was unquestionably traced to the personnel manager, who eventually presented himself for examination, which disclosed bilateral cavity formation. By his own admission, he had been tuberculous for years.

The unsatisfactory results of prolonged bed and postural rest, and the danger of delayed closure of cavities demand the immediate utilization of other methods of hastening recovery in this type of case. If no signs of improvement are seen after a reasonable trial of bed rest, postural rest and shot-bags, other methods of obtaining the needed relaxation for the lung

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should be employed without further procrastination. The proposed operative procedures are those included under the term "collapse therapy," their basis consisting in providing rest for the lung through its collapse. This paper does not allow a full discussion of these methods, many of which are of questionable merit; therefore, my remarks will be confined only to those having widespread acceptance and known to be of established value, with a superior background of experience; namely, artificial pneumothorax, intrapleural pneumolysis, phrenic neurectomy and thoracoplasty. Extrapleural pneumolysis, intercostal neurectomy, scaleniotomy and direct cavity drainage are applicable in a few selected cases. This contribution is based upon 25 years' experience with artificial pneumothorax, during which time approximately 1700 cases have been subjected to it; in addition, about 1000 cases have had the benefits of such surgical collapse procedures as intrapleural pneumolysis, phrenic neurectomy and thoracoplasty. Extrapleural pneumolysis and direct cavity drainage were employed in a few cases.

When collapse therapy has been decided upon, the first method to be considered should be artificial pneumothorax, although some surgeons still contend that thoracoplasty is the method of choice. But I do not believe such statements come from those having pneumothorax experience, as, among the latter, the feeling is predominant that every candidate for collapse therapy should be granted a pneumothorax trial.

Artificial Pneumothorax

Artificial pneumothorax is the simplest and most efficient method of putting the lung at rest by collapse. One great disadvantage, however, is the necessity of protracted continuation of the collapse, whereby the treatment often becomes a tiresome affair for the patient; yet, if all goes well, the patient ultimately has a good functioning lung instead of a permanently collapsed one,—as will be the case if major surgical procedures are adopted.

The danger of complications in pneumothorax is negligible; less than 2 per cent of our series died as a result of complications. Since using carbon dioxide for primary inflations, we have not had a gas embolism in 10 years.

Artificial pneumothorax should be used much earlier than is generally the custom. It is indicated in pulmonary tuberculosis with beginning infiltration and a positive sputum, as well as in moderately advanced cases. If no amelioration is forthcoming from a three to five months' routine of strict sanatorium care, and if clinical and roentgenologic study reveals a progression of disease, or at least the response to treatment has been unsatisfactory, a pneumothorax should be attempted at once. A good general rule is to induce a pneumothorax on every cavity case, unless there is some contraindication. When it is known which lung is the source of bleeding, hemoptysis is an obligatory indication for pneumothorax. Tuberculous pleurisy with effusion should be aspirated and continued as a controlled pneumothorax. This is also the best procedure to follow with tuberculous

spontaneous pneumothorax. Exudative types of tuberculosis are no contraindication—good results will be obtained, provided a satisfactory collapse is established, notwithstanding arguments that the consolidated lung cannot be collapsed. This is admitted; but if the patient survives the softening phase, the lung will at least be separated from the chest wall and active collapse can follow as excavation takes place. We have seen this successful time after time.

The contraindications include renal or cardiac failure and extensive emphysema. Tuberculosis of the larynx and intestines, unless uncontrolled and causing a significant hindrance in the patient's nutrition, is no contraindication; neither is controlled diabetes a contraindication.

My associates and I have often called attention to the constituents upon which successful pneumothorax therapy depends, but they may be repeated here. According to our experience, determining factors are: (first) the type of disease, its character, degree of activity, complications and condition of the opposite lung; (second) the character of the pneumothorax; (third) social and environmental conditions influencing the length of treatment. If the latter issue is satisfactory, the results of treatment will depend (first) on the type of disease; (second) on the character of the pneumothorax; (third) on the condition of the opposite lung. Admittedly, cases with the disease confined to one side are preferable. But the presence of even active disease in the contralateral lung is not a contraindication per se. We have repeatedly witnessed the healing of a contralateral lung lesion following establishment of a satisfactory pneumothorax on the homolateral side. Cases with a more or less stationary cavity on one side, with progressive bronchogenic extension to the opposite lung, can best be treated by establishing a pneumothorax on the side of the fresh invasion. As collapse on the newly invaded side progresses, and if the mediastinum is mobile, it will shift and fibrosis will proceed on the cavity side. We have had numerous successes by following this technic. There should be no hesitancy in closing cavities as soon as possible by progressive collapse or compression, instead of relying upon partial or selective collapse in this type of case.

In fully 20 per cent of cases selected for pneumothorax, dense pleuritic adhesions will prevent any gas introduction; these require other surgical intervention (noted later), unless contraindications are present. Several years ago we analyzed a group of cases of the above type, wherein a pneumothorax was indicated but adhesions prevented any gas introduction. These cases were subjected to extended sanatorium care, with the result that less than 7 per cent recovered. Had the advantages of modern surgery been attainable, I am certain that fully 40 to 50 per cent would be alive and well.

In a second group of cases studied, pleuritic adhesions prevented sufficient functional rest and closure of cavities in approximately 40 per cent. While gas was introduced and a partial pneumothorax established, recovery followed in no more than 15 per cent. Thus, in 60 per cent of cases selected

for pneumothorax, it either cannot be used, or satisfactory collapse cannot be obtained. This latter class of case is perhaps subject to more debate as to the program to be followed than any other.

We have frequently seen unfortunate instances wherein an unsatisfactory collapse was continued for a lengthy period when it could be clearly shown that pleuritic adhesions inhibited closure of a cavity; undoubtedly, a small number of such cases will recover, but eventually in the majority, extension of disease into the opposite lung becomes manifest, or, if already present, such critical inroads will have been made that the patient's state is hopeless. It is painful to realize that the disease process is allowed to advance in so many cases when the advantages of surgery, if used earlier, would be so beneficial.

In a third group of cases subjected to pneumothorax the collapse was a satisfactory one—often in spite of adhesions—and approximately 50 per cent recovered. If one could persuade the patient to continue the pneumothorax for an appropriate length of time, and to give proper coöperation in taking the cure, the number of recoveries would be decidedly increased. That pneumothorax should be withheld until after a probation of sanatorium care is not in keeping with the advances made in the treatment of this disease by collapse therapy. Too many sanatoria do not utilize collapse therapy beyond artificial pneumothorax, and their first gesture toward surgery is confined to phrenic neurectomy. Beyond that, many institutions are unprepared to carry out the necessary collapse therapy program.

This brings me to a consideration of the surgical treatment of adhesions, —that is, the conversion of an unsatisfactory pneumothorax, because of adhesions, into a satisfactory one. We have never regarded the open operation appropriate for severing adhesions, but for years we did advocate active stretching of adhesions by gradually increasing the intrathoracic pressure—with end results that were far from satisfactory. In 1925, we adopted the closed intrapleural pneumolysis proposed by Jacobaeus, and I later modified it by substituting the high-frequency current for cutting purposes in place of the galvanocautery, which was defective because of the patient's reaction to operation, the character of cutting, and the too frequent incidence of complications.

As already stated, an uncollapsed cavity is a menace to the patient and others in close contact. If efforts to close tuberculous cavities by artificial pneumothorax have been defeated by adhesions, and the patient still raises a positive sputum after three to five months, one should consider surgical attack upon the retarding adhesions at once.

Intrapleural Pneumolysis

There is need of a better understanding on the part of those who ignore this most neglected of collapse therapy procedures. A tuberculosis specialist with no surgical training hesitates at attempting the operation—and rightly

so—for, while it is not difficult, some surgical training is necessary to prevent and combat complications which might arise. The surgeon undertakes it reluctantly because he lacks a pneumothorax experience, and often has no knowledge of thoracoscopy. Unaccustomed to operating under the guidance of the thoracoscope, and believing he can more accurately visualize the operative field, he prefers the open method of severing adhesions.

The open operation, however, is unnecessary, because one can place the thoracoscope in such a position as to afford examination of every part of the pneumothorax cavity, which is impossible with the unaided eye. After experience, one can recognize the structure of tissues much better with the thoracoscope and confidently sever large adhesions that could not be cut by the open operation without great risk to the patient.

The dangers of hemorrhage, bronchopleural fistula and empyema are slight when proper technic is employed. While we have given up the galvanocautery of Jacobaeus in favor of my electrosurgical method, we do not condemn the cautery as dangerous—we simply believe the electrosurgical method, while perhaps technically more difficult, is the method of choice because the undesirable aspects of the galvanocautery are excluded.

The operative technic has been fully discussed previously.[1, 2, 3, 4] For those uninformed about the operation, I will briefly state that in the closed intrapleural pneumolysis, instead of making the opening through the chest wall, after the resection of ribs, sufficiently large to permit surgical ligation and cutting of adhesions—which, after all, is a major operation for the patient—a site is selected for introducing the thoracoscope and after local anesthesia infiltration of that area, the optical instrument (thoracoscope) is introduced by means of a trocar and cannula. A study is then made of the pneumothorax cavity and a site selected for similarly introducing the cutting instrument under local anesthesia through a chest wall puncture. For additional enlightenment, I would refer to my publications.

Technically, as far as the patient is concerned, the operation is a very minor one, scarcely less objectionable than a pneumothorax refill or diagnostic puncture. Adhesions will be present in almost half of the cases selected for pneumothorax treatment, but they will not necessarily prevent a satisfactory collapse or compression of the lung, hence, the mere presence of adhesions is no indication for operation.

Intrapleural pneumolysis is indicated where roentgenologic and clinical evidence discloses (after three to five months' trial) that adhesions are retarding a satisfactory collapse of the lung, provided one can assume that recovery will take place after a satisfactory pneumothorax has been established. Furthermore, adhesions must be of an operable type, and the pneumothorax sufficiently large to permit manipulation of instruments. The operation is also indicated when uncomfortable symptoms from downward pressure on the stomach and liver are apparent (even in satisfactory pneumothorax) in endeavors to maintain a proper collapse by high intrathoracic pressure. A still further indication is one wherein adhesions have

become fibrous and are causing an early expansion of the lung by their contraction,—thus often inciting hemorrhage or recurrence of tubercle bacilli in the sputum.

Complications. In over 250 cases operated upon we have had no direct operative mortality. In our series only one death occurred for which the operation was indirectly responsible. We had three profuse hemorrhages early in our work but no instance of serious sequelae. Serous, hemorrhagic and purulent exudate occurred much too frequently while utilizing the galvanocautery of Jacobaeus. This and other disadvantages led me to perfect the instruments and adopt the high frequency method then widely applied in general surgery. Our first experience with the high frequency method, although superior to the galvanocautery, left much to be desired in the type of unit employed. When the Bovie Electrosurgical Unit * appeared on the market, with its new features for the control of bleeding, we tested it experimentally. Finding it fulfilled all requirements, we have since used it routinely, and attribute to the advantages of this unit our present low incidence of serous exudate (3.8 per cent), purulent exudate (2.5 per cent), and hemorrhagic exudate (1.2 per cent). Severe febrile reactions no longer occur.

The general conception of this operation is that only small adhesions, the size of one's finger, may be severed with safety. However, I have had repeated success in severing adhesions as large as the palm of the hand of an average man,—without hemorrhage or deleterious complications.

In a series of over 250 cases, 70 per cent have been clinically successful,—that is, the unsatisfactory collapse was converted into a satisfactory one and all patients were restored to working capacity with a negative sputum; whereas, before operation, over 90 per cent had a positive sputum and 85 per cent were bed cases.

Intrapleural pneumolysis is attracting the attention it justly deserves. Were it utilized to the extent it merits, fewer thoracoplasties would be performed on the class of cases wherein a pneumolysis is appropriate. We are convinced that three to five months' trial will determine the efficacy of a pneumothorax. If, after that period of time has elapsed, roentgenograms show evidence that adhesions are preventing closure of cavities, a thoracoscopic examination, which is as harmless as a pneumothorax refill, should be made to determine their operability. Adhesions found suitable for operation should be severed. If inoperable types are present, the useless pneumothorax should be discontinued and other surgical collapse procedures promptly put to use before the case is too far advanced.

Phrenic Neurectomy

While intrapleural pneumolysis is the most neglected operative collapse procedure, one may reasonably state that phrenic neurectomy undoubtedly is the most abused. In 1912, Stuertz proposed resection of the phrenic

* Manufactured by The Liebel-Flarsheim Co., 303 West Third St., Cincinnati, Ohio.

nerve to paralyze artificially the hemidiaphragm on the diseased hemithorax to provide functional rest of the lung. Resection of the nerve was followed by atrophy of the musculature of the diaphragm and its gradual rise into the thorax. Collapse of the lung, amounting to one-fourth to one-third its volume, took place.

The original operation was relatively short-lived; in approximately one-half to one-third of the cases, the diaphragm paralysis was of short duration or failed to occur at all. When the anomalies of the phrenic nerve became known, through the work of Felix and Goetze and confirmed by Plenk and myself, two operations were proposed—the exairesis of Felix and the radical phrenicotomy of Goetze. Space does not permit a discussion of the merits of these two operations.

Based on the anatomical studies of Plenk and myself,[5] the preferable approach to the phrenic nerve is through the subclavian triangle. One is thus in a position safely to evulse the nerve, as well as sever accessory nerve fibers, if encountered. It is unnecessary to remove the entire nerve, as we find that an 8 to 10 cm. length is sufficient to give a permanent paralysis.

Phrenic neurectomy is a minor operation, and while anomalies of the nerve exist in more than 25 per cent of cases, it is amazing that more complications do not occur. The operation should not be undertaken without a thorough knowledge of the topographical anatomy of the neck and familiarity with variations of the phrenic nerve. Ignorance of phrenic abnormalities is responsible for many accidents during operation, and fatal results have occurred even in the hands of competent surgeons. Damage to the vagus and sympathetic trunk is not uncommon,—also instances have been cited where no phrenic nerve was found. We, ourselves, have operated upon five patients who were referred to us after previous unsuccessful attempts by others to locate the phrenic nerve. In each case we found the phrenic nerve arising from the fifth cervical root far lateral to the scalenus anticus. A recent consultation had to do with a patient from whom a surgeon had removed a section of what was thought to be the phrenic nerve. The patient developed a Horner syndrome, but the diaphragm functioned normally. A second surgeon later reoperated upon the same case, and removed a section of a nerve—supposedly the phrenic—and the patient promptly exhibited a unilateral paralysis of the vocal cords. The diaphragm, however, still functioned normally. Certainly, such accidents should be avoided.

Indications. The indications for phrenic neurectomy are:

As an independent procedure in all cases wherein an artificial pneumothorax is indicated and attempts to introduce gas have proved futile or insufficient because of inoperable pleuritic adhesions which cannot be severed by the closed method of intrapleural pneumolysis; for social or economic reasons in cases when a prescribed course of pneumothorax is not possible.

Before every thoracoplasty because the improvement following an induced hemidiaphragmatic paralysis may be so marked as to avert the neces-

sity of a major surgical operation. A satisfactory hemidiaphragm paralysis (in favorable cases) occasions such improvement that the patient is rendered a far better surgical risk; also the sputum quantity and cough are markedly diminished, thus minimizing the danger of aspiration infection if a thoracoplasty is done. Its employment before thoracoplasty is also indicated since, by providing as much collapse as possible through the rising diaphragm, one may be able to reduce the number and length of ribs to be removed later. Through its use also the heart accommodates itself in stages to the increased functional activity that will be demanded of it as a result of thoracoplasty.

The value of phrenic neurectomy is indisputable as a supplement to artificial pneumothorax (for additional collapse) where non-operable adhesions are preventing a satisfactory lung collapse, and also as a test of the soundness of the contralateral lung. In cases with suspicious changes in the better lung, some surgeons are of the opinion that a phrenic neurectomy is of greatest value as a " test " operation before a thoracoplasty. Should the physical or roentgenologic findings increase after phrenic neurectomy, with exacerbation of fever, or other perturbing manifestations, an extrapleural thoracoplasty is absolutely contraindicated. Contradictory to this belief, close scrutiny of our material corroborates the affirmation that the result of a phrenic neurectomy as a " test " operation, cannot be accepted with complete confidence, since we have seen a contralateral lung lesion withstand the " test " operation, but exhibit activity after a thoracoplasty. We have also observed an essentially negative contralateral lung exhibit disease following the " test " operation, but pass through a complete thoracoplasty undamaged, although the diseased area in the contralateral lung was essentially the same before each procedure.

Other indications are threatened early obliterative pneumothorax where phrenic neurectomy is used combined with oleothorax to maintain collapse; and in the treatment of empyema occurring as a complication of pneumothorax where it serves to lessen the area of pyogenic membrane; also toward the end of a course of pneumothorax therapy in a case with an originally very extensively diseased lung, in order to diminish the capacity of the hemithorax so that it may accommodate a lung which has been shrunken by scar tissue changes—thus lessening the danger of reëxpansion of excavated areas, secondary bronchiectasis, or retraction of heart and mediastinal contents.

Results. The limits of this dissertation do not permit an analysis of our entire series of approximately 500 cases of phrenic neurectomy, performed according to the various indications and clinical types of cases. Exudative types of tuberculosis should be excluded, as this form seldom derives any benefit. The best results are obtained in the fibrocaseous and fibrocaseous cavernous cases (provided the cavities are not too large), who are candidates for a thoracoplasty. Our experience in this type of case has been extremely gratifying, as 15 per cent of cases selected for thoraco-

plasty, who had a phrenic neurectomy as a preliminary operation, have recovered, rendering the thoracoplasty needless. We have frequently remarked that cavities in the apex heal as a result of a phrenic neurectomy alone, provided a good diaphragm elevation is obtained. However, if the diaphragm pursues a horizontal course and is fixed by dense pleurodiaphragmatic adhesions, no benefit can be expected.

One should await maximum elevation of the diaphragm before proceeding with a thoracoplasty, the required time being from three to six months. If it is obvious that a phrenic neurectomy alone will not provide sufficient rest and collapse of the lung for healing to take place, one may proceed with the thoracoplasty, after waiting sufficiently long to observe its influence upon the integrity of the opposite lung.

Extrapleural Thoracoplasty

This operation should not be regarded as a last resort procedure. Such a mistaken conception is often responsible for delaying the operation until the patient becomes a bad surgical risk. There is urgent need of education regarding the rôle of thoracoplasty, for the impression that it is a shocking deforming operation, with high mortality and scant hope of cure, is a greatly mistaken one and should be rectified. In essentially stationary cavity cases with a good contralateral lung, if after a reasonable trial of the rest cure attempts to establish a pneumothorax have been prevented by adhesions, or if a pneumothorax has been established and adhesions of an inoperable type prevent closure of the cavity, and a phrenic neurectomy has not obtained the desired results, a paravertebral extrapleural thoracoplasty should be decided upon, provided there are no contraindications. The best results will be secured in chronic fibrous tuberculosis with evidence of shrinkage. If cavities are present, the thicker the wall, the less favorable will be the outcome.

The contraindications for thoracoplasty are the same as for an artificial pneumothorax, with the exception that disease of the contralateral lung, concerning which some leniency may be exercised in relation to a proposed pneumothorax, is an absolute contraindication to thoracoplasty unless it be arrested and not extensive. Poor surgical risks should be excluded, particularly if the operation is undertaken in a tuberculosis sanatorium, as the loss of a case is discouraging to others facing the same operation. The presence of incurable or uncontrollable organic disease is also a contraindication for thoracoplasty.

The selection of cases must be much more rigid than for pneumothorax. Exudative types of tuberculosis are unsuited for thoracoplasty, and patients whose resistance to tubercle bacilli invasion is inadequate, permitting progressive extension of disease, usually are poor risks. Limitation of operation to the age of 45 or 50 years is unnecessary if clinical and laboratory

studies indicate that the patient is a good surgical risk. Our oldest patient was 62, with tuberculosis of 15 years' duration. She made a perfect recovery.

A case with a combination pneumothorax, with a large cavity being held open by diffuse adhesions, would seem to offer an ideal indication for thoracoplasty. Yet, our experience suggests the contrary,—especially if there is a mediastinal bulge to the opposite side. Collapse of the chest wall increases the hernia; moreover, the presence of the pneumothorax often prevents a satisfactory collapse of the chest wall. The outcome in the above type of case can be greatly improved by artificially stiffening the mediastinum by precipitating a pleuritis of the bulge. The technic is simple and harmless. The patient is placed on the table with the pneumothorax side up; then, the second intercostal space is anesthetized as for a pneumothorax refill, and 2 c.c. of 1 per cent oil of gomenol and paraffin are slowly injected so that it will flow into the hernia. The patient remains in the same position for one-half hour, after which 50 to 100 c.c. of normal saline solution are slowly introduced through the same puncture, so that it will likewise flow into the bulge. The gomenol will now float upon the salt solution. Next, the patient is seated upright and the salt solution with gomenol is aspirated through another puncture at the base—this procedure prevents the formation of a diffuse pleuritis. With a normal pleura, a slight febrile reaction with exudate will occur, but it will be mild and will last only a few days. If there is no reaction, the procedure is repeated, using 2.5 per cent gomenol in the same manner. Again, if no reaction takes place, one repeats the process, gradually increasing the strength of gomenol until a reaction does occur. It may even be necessary to increase the strength up to 10 per cent. A successful issue is indicated by a gradual return of the mediastinum to the midline. This simple method of fixing the mediastinum also renders the patient a better surgical risk by eliminating the danger of mediastinal flutter. We avail ourselves routinely of this method in the last named type of case. This procedure should usually precede a thoracoplasty by two or three months, or even longer; and should also come before the preliminary phrenic neurectomy has been performed.

If the pneumothorax is a small one, it is better to permit the lung to expand before attempting the thoracoplasty.

I have no intention of going into the technic of thoracoplasty, but some of the essentials ought to be pointed out. Routinely, in the presence of underlying disease in the upper half of the hemithorax, we perform the upper phase first; contrariwise, if the pathologic lesions are chiefly in the lower lobe, we do the lower phase first. The operation should be done in two or more sittings. For poor risk patients, we prefer the graded thoracoplasty suggested by Hedblom.

The length of segments and number of ribs to be resected must be individualized in each case—depending upon the underlying lesion and the condition of the patient. Adequate sections of ribs should be severed close

to the transverse processes. In a number of cases operated upon by others as well as in some of our early cases, the sections of ribs removed were too short; the cavities remained open and the removal of regenerated rib became necessary. This latter procedure is an altogether unpleasant one, as the removal of portions of regenerated rib sufficient to provide adequate collapse is sometimes a tedious operation. Because of the above error, one of our early cases was operated upon nine times before the cavity was successfully closed.

When large upper lobe cavities are present in a case with a pneumothorax, we routinely follow the upper phase operation by an accessory lateral one, including the first rib, then proceed with the lower phase, unless only a partial thoracoplasty is intended. We feel that a much better collapse of large cavities is effected by the above sequence of operation. Partial thoracoplasties on upper lobe cavity cases have often produced disappointing results, necessitating reoperation to secure a better collapse.

According to our experience, if the case presents a large cavity extending to the second rib in front, and if the lung over the cavity is diffusely adherent to the chest wall while the rest of the lung is completely collapsed by a pneumothorax, the upper phase operation should be done first, resecting, if possible, substantial segments of the upper five ribs and all of the first. During the operation, a 14 gauge needle should be left in position through the chest wall so that, as the chest wall falls in, air may pass out of the pleural cavity. The needle must be kept away from the operative field and withdrawn after the operation is completed. Within a week or 10 days the remaining portions of the above ribs are resected close to the sternum through a midaxillary incision. Between operations a film will indicate the advisability of aspirating air before the second operation, but a needle is again placed in position during the second operation to allow air to escape. Within a week or 10 days, the lower phase operation follows with the needle again in position. Following the completed thoracoplasty, air is aspirated at regular intervals and the chest wall tightly strapped to obliterate the pneumothorax. The patient is placed in the author's thoracic hammock as soon as possible to effect a better chest wall collapse during the period of osteogenesis and to prevent deformity.

In performing a thoracoplasty in combination with a pneumothorax, or in cases with free pleural space, one should exercise great caution in stripping the rib of its periosteum so as not to tear through the pleura and possibly invert a bleeding intercostal vessel into the pleural cavity. In case of such an accident one should make sure that no bleeding vessel is inverted before closing the torn place. I once witnessed this accident in the hands of a very experienced and clever thoracic surgeon. Although all visible bleeding in the wound was arrested at the time of operation, the patient died several hours later. Autopsy disclosed the cause of death: hemorrhage into the pleural cavity.

After a thoracoplasty has been decided upon, the patient is prepared for operation. If he has spent months at bed rest and has normal temperature, it is advisable to have him sit up in a reclining chair, increasing the hours day by day until six hours have finally been reached. Then short walks are given—provided, of course, that febrile reactions do not take place. This plan improves the cardio-respiratory tone. Complete laboratory studies should be repeated, and blood transfusion given if indicated. Blood chemical studies, kidney function tests and an electrocardiogram should be made. The patient should be trained in cavity drainage, the time noted when this is completed,—and the hour of operation then scheduled for a time when the cavity is essentially empty. One week prior to operation the patient is placed upon a protein-free, carbohydrate-rich diet with abundant water, and hard candy is sometimes given after meals. He is also prepared psychically for operation; and 24 hours before the procedure, he is placed in an oxygen tent for one-half hour out of every three for purposes of hyperventilation. We are sure that this plan has contributed much to our low operative mortality.

Preoperative medication in nervous and apprehensive patients consists in luminal, ortal sodium, or nembutal the night before operation to insure a good sleep. This medication may be repeated three hours before operation if necessary. One-half hour before operation we usually give ⅓ grain of pantopon, if there is no idiosyncrasy. In good surgical risk cases, with normal blood pressure, we often administer pernoston or sodium amytal intravenously in hypnotic doses. The operation is performed under local anesthesia with 1 per cent novocain-suprarenin, and light ethylene anesthesia. During operation a constant check is made upon the blood pressure, pulse and respiratory rate, and the moment any suggestion of shock appears, the operation is concluded. Until a few years ago, we made an effort to perform the operation quickly; since then, we take more time—25 to 30 minutes if all goes well. After operation the patient is again placed in the oxygen tent for 24 hours as before operation. Intravenous transfusion of blood, saline solution or acacia is given if necessary.

Nurses with special training should be in charge of these cases to support the chest wall during coughing and at the same time encourage the patient to raise the required amount of sputum. If necessary, opiates are used to control pain during the first two days following operation.

Before the next operation the case is carefully studied and prepared. As soon as possible after the completed posterior operation, the patient is placed upon the operated side in the thoracic hammock.[3] The hammock is elevated from the bed; this increases the chest wall collapse and prevents deformity. Daily resting (for several hours) in the hammock is continued for three months, during which time the chest is kept tightly strapped.

We have experienced no death from postoperative shock, wound infection or hemorrhage in our series of 150 cases. Three postoperative deaths within a week were due to cardiac failure. The remaining fatalities were

due to aspiration pneumonia, progressive tuberculosis in spite of the operation, or to tuberculosis of the intestines and from other causes not related to operation.

The results of a well performed thoracoplasty compare favorably with the results obtained from artificial pneumothorax. In our series of 150 cases upon whom 360 operations have been performed, the clinically well group totals 70 (46.6 per cent). The improved group comprises 36 cases (24 per cent). They are capable of working but tubercle bacilli are occasionally found in the sputum. No doubt half will recover. In nine (6 per cent) who still have a positive sputum it is probable that additional collapse will be necessary. Three (2 per cent) have died as a direct result of the operation from cardiac failure; 14 (9.3 per cent) died of causes indirectly due to operation, such as aspiration pneumonia; 18 (12 per cent) died of causes not related to the operation, such as intercurrent disease, accidents, etc.

The results of surgical treatment of pulmonary tuberculosis are stimulating, and it is extremely gratifying to know that every tuberculosis sanatorium or hospital where tuberculosis is accepted has a number of patients who can be restored to health and self-support by the application of modern thoracic surgery, instead of being left to await a certain dissolution of soul and body.

There has been a gradual awakening on the part of those accepting the responsibility for the treatment of pulmonary tuberculosis to the fact that collapse therapy, particularly surgery, offers a hope unattainable by the routine sanatorium regimen. The application of collapse therapy to the fullest extent that it is indicated would be facilitated by better coöperation between the medical tuberculosis specialist and the thoracic surgeon, in institutions where a strictly medical and surgical service exists, and requires transfer of cases for operation from one service to the other. The ideal situation exists when the phthisiotherapist is qualified by training and experience to assume entire responsibility from both the medical and surgical standpoint so as not to necessitate, as it were, the changing of pilots in midstream. Successful collapse therapy, similar to urology, laryngology, and gynecology, is largely a one-man job. I predict that the tuberculosis specialist of the future will have both adequate medical and surgical training to conduct the treatment of pulmonary tuberculosis according to the indications and will not, as is now often the case, call in the thoracic surgeon when the case has become too far advanced for surgical relief.

The material referred to in this contribution is from the combined service of myself and associates, Dr. Ray W. Matson and Dr. Marr Bisaillon.

BIBLIOGRAPHY

1. Matson, R. C.: Cauterization of adhesions in artificial pneumothorax by Jacobaeus-Unverricht method of closed pneumolysis; observations on 100 cases, Am. Rev. Tuberc., 1929, xix, 233–305.

2 MATSON, R. C.: Electrosurgical method of closed intrapleural pneumolysis in artificial pneumothorax, Arch. Surg., 1929, xix, 1175–1192.

3. MATSON, R. C.: Operative collapse therapy in treatment of pulmonary tuberculosis, West. Jr. Surg., 1930, xxxviii, 743; 1931, xxxix, 13.

4. MATSON, R. C.: Severing adhesions in artificial pneumothorax by electrosurgical method, Surg., Gynec. and Obst., 1934, lviii, 619–629.

5. PLENK, A., and MATSON, R. C.: Zur Phrenicotomiefrage. Beiträge zur Klinik der Tuberkulose, Band 62, Heft ¾, 1925.

OBSERVATIONS ON THE DIAGNOSIS AND TREATMENT OF PERIPHERAL VASCULAR DISEASE*

By EUGENE M. LANDIS, *Philadelphia, Pennsylvania*

FOR the diagnosis, prognosis, and effective therapy of peripheral vascular disease it is essential to divide patients into two groups: (a) those whose symptoms are due to simple spasm with no, or at most slight, organic vascular obstruction; and (b) those whose symptoms are due primarily to advanced organic disease of the arteries. Recent advances in the surgery of the sympathetic nervous system have made it highly desirable to detect, early in the course of peripheral vascular disease, whether the flow of blood to an extremity is diminished by simple arterial spasm, or by obliterative structural disease of the arteries. In treatment the best results can be obtained only if beginning organic occlusion is discovered before it has reduced too greatly the normal capacity of the blood vessels to dilate.

The several tests available for detecting early organic vascular obstruction, though different in method, are similar in principle. The surface temperature of the cold, exposed extremity is measured thermoelectrically. Vasoconstrictor tone is then abolished in the part under observation and the rise in surface temperature is recorded. The level to which skin temperature rises during complete vasodilatation has been determined in persons with normal peripheral circulation. If the surface temperature fails to reach this normal level in a room at suitable temperature, it can be concluded that the arteries supplying the part are unable to dilate owing to organic changes in their walls.

Vasodilatation of the peripheral vessels may be induced by many procedures, but we have chosen to use the simple expedient of immersing two extremities in warm water [1, 2] verifying abnormal findings in most instances by anesthetizing the posterior tibial nerve.[3] In completely normal subjects, immersing the forearms for 35 minutes in water at 43 to 45° C. dilates the cutaneous vessels of the lower extremities and elevates the surface temperature of the toes to 31.5° C. or more. Conversely, immersing both feet and legs in warm water for 35 minutes normally elevates the surface temperature of the fingers to 31.5° C. or more.

Patients with coldness, blueness or pain in the lower extremities who show under suitable conditions a normal elevation of skin temperature (i.e. to 31.5° C. or more) are certainly free from significant organic arterial obstruction (figure 1). When skin temperature fails to reach 31.5° C. but still reaches 26° C. or more (figure 2) only a moderate grade of organic occlusion is present. In such patients considerable benefit can be expected from contrast baths, local heat, diathermy, vasodilator drugs, the warm

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The expenses of this study were defrayed in part by a grant from the Philadelphia Heart Association.

cradle or sympathetic ganglionectomy, all of which increase blood flow, temporarily or permanently, by dilating those vessels which are still capable of expansion.

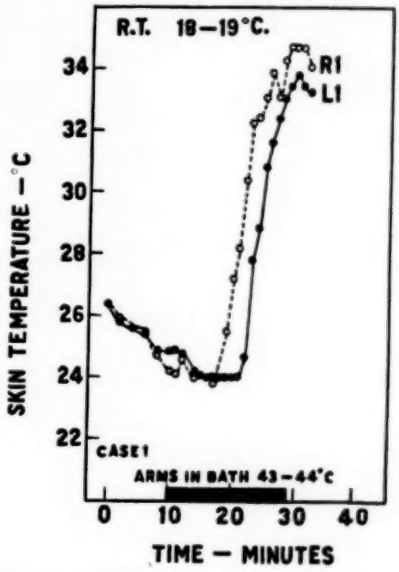

FIG. 1. Normal vasodilator response observed in a patient with bilateral thrombophlebitis. In this and subsequent charts L1 and R1 indicate the skin temperature of the left and right great toes, respectively; R. T., the room temperature. The shaded area below indicates the period during which the forearms were immersed in warm water. (From Landis and Gibbon,[2] by permission of the *Archives of Internal Medicine.*)

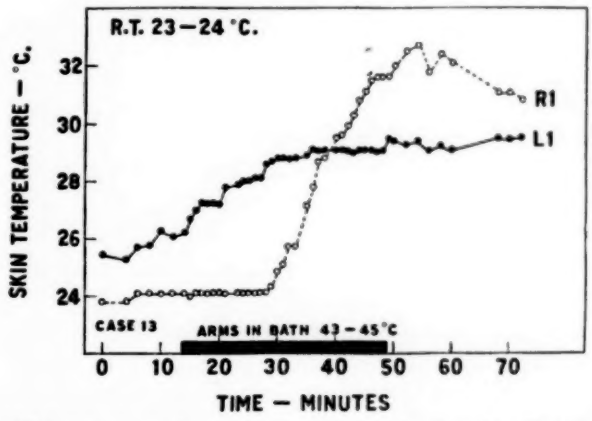

FIG. 2. Vasodilator response in a patient with arteriosclerosis. The response was only partial in the left foot and was much delayed in the right foot. (From Landis and Gibbon,[2] by permission of the *Archives of Internal Medicine.*)

In the advanced stages of peripheral vascular disease the arteries become more or less rigid owing to structural changes in their walls. These diseased vessels have not only abnormally small lumina but they may be unable

to dilate even when vasoconstrictor tone is abolished. Skin temperature then fails to rise (figure 3) during the period when vasoconstrictor tone is

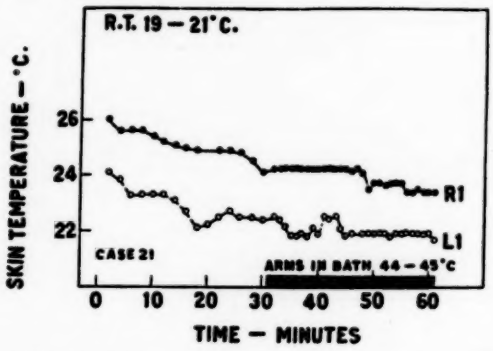

FIG. 3. Chart showing complete absence of vasodilator response in a patient with advanced diabetes and arteriosclerosis with gangrene. (From Landis and Gibbon,[3] by permission of the *Archives of Internal Medicine.*)

abolished. After the arteries have thus lost their power of dilating, the therapeutic procedures mentioned previously cannot be expected to increase blood flow and, in fact, they usually fail to improve the nutrition of the tissues in the extremity. Eventually many of these patients with conspicuous organic occlusion suffer from trophic changes, ulceration and gangrene, leading finally to amputation. Such patients present a particularly harrassing therapeutic problem since the usual methods of increasing peripheral circulation all depend fundamentally upon the residual power of vasodilatation. At the University of Pennsylvania we have been interested during the past three years in the problem of attempting to increase peripheral blood flow in this unfavorable group of patients. It can be expected that any procedure which increases blood flow in spite of advanced organic occlusion will reduce pain, aid healing, and delay or possibly prevent the appearance of gangrene. Rest pain and ulceration frequently require the amputation of extremities which, if they could be preserved, would prevent the patient from becoming an economic liability.

Poiseuille, early in the last century, described the laws which control the flow of fluid through a rigid tube. He observed that the amount of blood flowing through a capillary tube depends upon the fall in pressure along the tube. This relationship can be demonstrated clearly in the living animal by measuring simultaneously capillary blood pressure and the rate of blood flow in single capillaries of the frog's mesentery.[4] Inserting a minute glass pipette into a single capillary makes it possible to follow the variations in capillary blood pressure which result from spontaneous arteriolar dilatation and constriction. Though capillary blood pressure varies considerably, venous pressure remains approximately constant. The drop in pressure from the capillary to the vein, represented in figure 4 by the shaded vertical columns, can be at one moment very small, at another quite

large. The rate at which blood flows through the observed capillary follows faithfully each variation in capillary blood pressure. In other words, when capillary and venous pressures are equal the drop in pressure along the capillary is minimal and blood flow ceases. On the contrary, when the drop

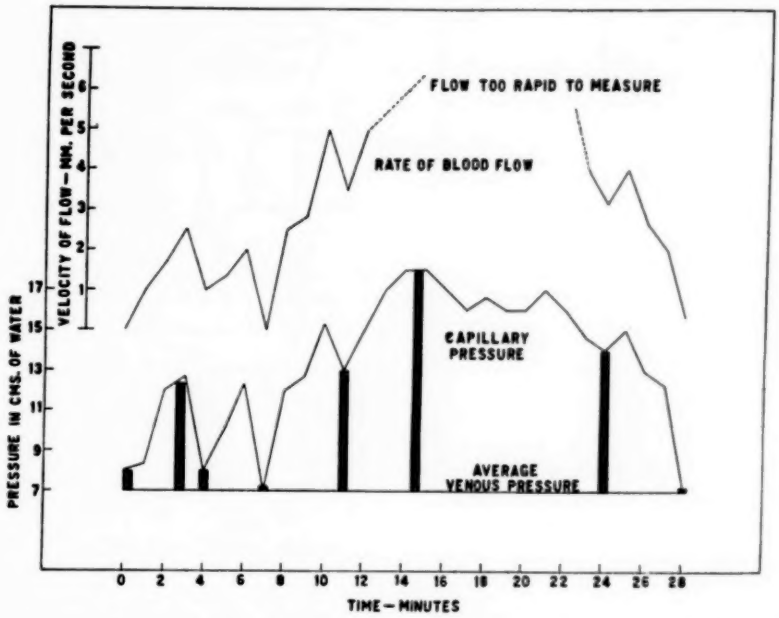
FLOW TOO RAPID TO MEASURE
RATE OF BLOOD FLOW
CAPILLARY PRESSURE
AVERAGE VENOUS PRESSURE
VELOCITY OF FLOW — MM. PER SECOND
PRESSURE IN CMS. OF WATER
TIME — MINUTES

FIG. 4. Showing relation between capillary blood pressure and the rate of blood flow in a single capillary of the frog's mesentery. (From Landis,[4] by permission of the *American Journal of Physiology*.) The vertical shaded areas represent the drop in blood pressure from capillary to vein.

in peripheral blood pressure is large, flow may become too rapid to measure microscopically. Thus, it may be expected that, if the peripheral drop in blood pressure be increased artificially, blood flow may be made greater.

In the presence of a rigid system of arteries, incapable of dilatation, the total fall in pressure in the peripheral vascular system may be increased in two ways, (a) by elevating systemic blood pressure, or (b) by diminishing venous pressure. The first method is generally impracticable for numerous and obvious reasons. It seemed possible, however, that applying negative pressure periodically to the skin of the extremity might increase blood flow by temporarily reducing venous pressure below atmospheric pressure.

An aluminum box was built large enough to accommodate the lower extremity to a point six inches above the knee where the thigh was surrounded by an air-tight rubber cuff (figure 5). An air pump, valve, mercury manometer, and relay were so arranged that the lower extremity was exposed alternately and automatically to a negative pressure of 80 to 120 mm. Hg for 25 seconds and a positive pressure of 60 to 80 mm. Hg for five

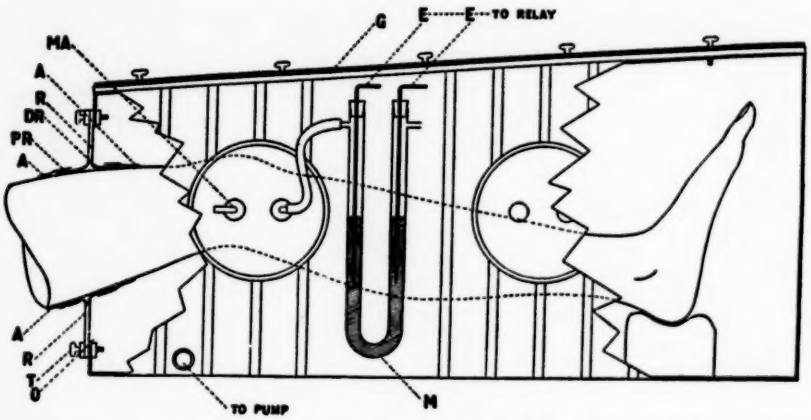

FIG. 5. Diagram of aluminum box and double cuff (PR, DR) used for applying suction and pressure to the surface of the lower extremity. (From Landis and Gibbon,[6] by permission of the *Journal of Clinical Investigation.*)

seconds. Figure 6 indicates diagrammatically the rapidity with which pressure is changed, only 3 seconds being required for the shift from +80 mm. Hg to —120 mm. Hg. The normal difference between mean arterial and venous blood pressures is about 80 mm. Hg. During suction this peripheral drop in blood pressure (vertical shaded areas in figure 6) is

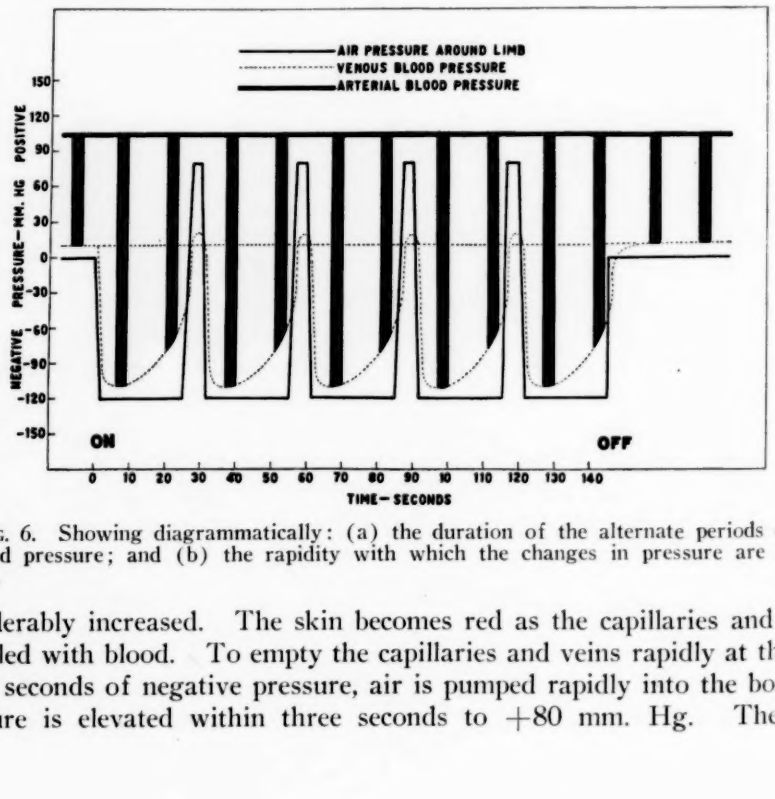

FIG. 6. Showing diagrammatically: (a) the duration of the alternate periods of suction and pressure; and (b) the rapidity with which the changes in pressure are accomplished.

considerably increased. The skin becomes red as the capillaries and veins are filled with blood. To empty the capillaries and veins rapidly at the end of 25 seconds of negative pressure, air is pumped rapidly into the box and pressure is elevated within three seconds to +80 mm. Hg. The skin

blanches and the vessels are emptied through the veins to afford a reservoir into which fresh arterial blood may be drawn by the next period of negative pressure. The net result of this alternating suction and pressure is to increase considerably the average drop in blood pressure from artery to vein. Theoretically this should increase proportionately the flow of blood through the peripheral vessels of the extremity.

Prolonged ischemia produces local coldness, cyanosis, intermittent claudication, rest pain, and eventually ulceration or necrosis of tissue. If it is true that suction and pressure increase the local supply of arterial blood, these manifestations of ischemia should be relieved, at least to some degree. Landis and Gibbon [5, 6] showed in normal subjects under carefully controlled temperature conditions that blood flow, as indicated by skin temperature, was greater in the limb exposed to pressure variations. It was concluded that to obtain maximal effects on blood flow it is advisable to have (1) relatively brief periods of suction, (2) intermittent brief periods of pressure, and (3) diminished vasoconstrictor tone, the last being necessary in order that the reservoir for accommodating blood drawn in by each suction period might be adequate.

This paper comprises a brief summary of the effects of suction and pressure on the various manifestations of reduced blood flow in a series of 16 patients with advanced peripheral vascular disease. The disease was, in each instance, of long standing; the patients suffered from thromboangiitis obliterans, simple arteriosclerosis, or diabetes with arteriosclerosis. Twelve of these patients had no vasodilator response in the observed extremity, while the remaining four showed in the most severely involved extremity a rise of skin temperature to between 24 and 27° C.

With the patient semi-recumbent, the most severely involved extremity was exposed to pressure variations for periods of one to two hours, from twice daily to once weekly, for totals of 2 to 112 treatment hours. Suction was between —80 and —120 mm. Hg, pressure between +60 and +80 mm. Hg. Suction and pressure were applied alternately for 25 and 5 seconds, respectively, except in one instance in which intervals of 50 and 10 seconds were used for part of the time. (Table 3, Patient C3.) When skin temperatures were measured conditions were carefully controlled as described previously.[6] Vasoconstrictor tone was reduced by enclosing one forearm in an electric heating pad kept warm enough to produce slight generalized sweating.

Table 1 presents a summary of a series of short observations on the effects of suction and pressure on skin temperature. In every instance the foot which was exposed to pressure variations became warmer than the control extremity. The final temperature reached was always above that attained by the extremity when maximal vasodilatation was produced by abolishing vasoconstrictor tone. The digits of the foot exposed to suction and pressure became, on the average, almost 6.0° C. warmer than the untreated, or control, digits. The smallest difference in temperature was

TABLE I

The Effects of Suction and Pressure on Skin Temperature in Patients with Peripheral Vascular Disease

Patient No.	Side	Vasodilator response	Duration of application of suction and pressure	Temperature of digits		Rise in temperature
				Before treatment	After treatment	
			min.	° C.	° C.	° C.
1	R	none	59	22.2	30.5	8.3
	L	none	none	21.0	23.6	2.6
	R	none	none	23.5	27.0	3.5
	L	none	111	20.7	30.2	9.5
2	R	to 24° C.	81	19.4	31.9	12.5
	L	to 26° C.	none	19.8	22.5	2.7
3	R	none	41	24.4	28.1	3.7
	L	none	none	24.3	25.8	1.5
4	R	none	27	26.3	30.3	4.0
	L	none	none	30.3	29.8	−0.5
5	R	to 30° C.	none	26.0	26.2	0.2
	L	to 27° C.	120	25.8	31.8	6.0
	R	to 30° C.	none	21.5	24.2	2.7
	L	to 27° C.	120	21.8	30.9	9.1
			Average	Treated extremities		7.6
				Untreated extremities		1.8

2.2° C. (Patient 3), the largest 9.8° C. (Patient 2). The difference between the skin temperatures of the treated and untreated extremities was usually large enough to be perceptible to the hand of the examiner, and to the patient himself.

Skin color was estimated according to the Lewis [7] scale in which XV and XVI correspond to complete cyanosis, V to bright hyperemia, and VII or VIII to normal skin color. In areas of frank gangrene (table 2) no change in color could be detected, probably since the affected vessels were already thrombosed and circulation was at complete standstill. The digits of patients with severe pain, with or without ulceration, were more or less cyanotic. In some it required but a few alternations of pressure to change this cyanosis to normal skin color. The skin then became deeply red during suction and pale during pressure as does normal skin. Small areas remained cyanotic for several days, but the normal coloration eventually

TABLE II

Effects of Suction and Pressure on Skin Color in Patients with Peripheral Vascular Disease

A. With areas of frank gangrene.
Patient 1. No definite color changes XV
2. No definite color changes XV
3. No definite color changes near lesion XVI–XV. Remote areas of skin XII to X
4. Doubtful changes near lesion XV. Other areas XI to VII

B. With indolent, painful ulcers but no frank gangrene.
Patient 1. XII to VII
2. XIII to VII
3. IX to VII
4. IX to VII
5. XI to VIII
6. XIII to VII
7. XIII to VII

C. With pain alone.
Patient 1. XII–XIII to VIII
2. XIV to VIII
3. XII to VII
4. X–XIV to VII–VIII

extended over the whole skin surface. The hyperemia produced during the first few alternations in pressure is maintained for some hours, and usually becomes more and more lasting as treatment continues. In some, however, cyanosis persisted in the intervals between treatments. In three instances striking improvement in skin color has been followed during the winter and has remained in spite of severe cold.

Most of these patients suffered also from severe and often intractable rest pain, which was either constant or occurred in brief episodes, usually worse at night. Two types of observations may be summarized. First, to observe acute effects extremities were exposed to pressure variations during episodes of pain. Protocols 1 and 2 indicate the relief of pain

ACUTE EFFECTS OF SUCTION AND PRESSURE ON REST PAIN

Protocol 1. Patient had thromboangiitis obliterans with large gangrenous slough in palm following amputation of finger in another hospital. Patient was unable to keep hand above the level of the sternum owing to excruciating rest pain.

12:15 p.m. Pain present. Hand placed above level of sternum in modified box. Suction (80 mm. Hg) and pressure (60 mm. Hg) applied for 25 and 5 seconds, respectively.

12:30 p.m. No pain.

1:45 p.m. No pain,—pump stopped for 2 minutes. Severe pain in palm.

1:47 p.m. Pump started again.

1:48 p.m. Pain less.

1:49 p.m. Pain gone,—itching remains.

2:30 p.m. Hand removed from box. Pain recurred after patient returned to ward.

Protocol 2. Patient had arteriosclerosis and ulceration of two toes with rest pain preventing sleep in spite of sedatives.

11:00 p.m.	Severe pain wakened patient.
11:45 p.m.	Pain still present. Patient placed in apparatus with suction (120 mm. Hg) and pressure (80 mm. Hg) for 25 and 5 seconds, respectively.
12 midnight.	Pain gone, patient drowsy.
12:50–4:15 a.m.	Patient sleeping.
4:15 a.m.	Leg removed from apparatus. Patient slept remainder of night.

obtainable. The first patient was unable to keep the hand higher than the sternum owing to severe rest pain. At 12:15 p.m., when pain was present, the hand and forearm were placed in the apparatus so that they lay in a position known to produce pain. Fifteen minutes after pressure variations had begun the pain disappeared although holding the hand in the same position was unbearable under ordinary conditions. The pain remained absent until 1:45 p.m. when the pump was stopped for two minutes. This was followed by severe pain in the palm. Starting the pump again caused the pain to disappear leaving only some residual itching. Pain was absent for the remaining hour of the observation. The pain returned, however, several hours after suction and pressure were discontinued, and amputation was done primarily on account of the size of the slough. Another patient (protocol 2) had ulceration with severe rest pain due to arteriosclerosis. This pain had prevented sleep, in spite of moderate sedation, in the hospital. At 11:00 p.m. severe pain wakened the patient; the affected extremity was placed in the apparatus at 11:45 p.m., while pain was still present. Fifteen minutes later the pain had disappeared and the patient was drowsy. Thereafter he slept until 4:15 a.m., when he was removed from the apparatus and continued sleeping during the remainder of the night.

In the many hours during which extremities have been exposed to these pressure variations true rest pain has not been observed during treatment. Discomfort sometimes appeared owing to drying of ulcers. This can be avoided by covering the raw surfaces with vaseline. As a rule patients, previously exhausted by continued pain, fall asleep almost immediately after the extremity is placed in the apparatus. The continuous application of negative and positive pressure over long periods of time was attempted. It was found quite early, however, that the rubber cuff at the proximal end of the apparatus became uncomfortable usually after two to four hours, making it impossible to prolong pressure variations uninterruptedly beyond this period.

While temporary relief of pain was obtained even when areas of frank gangrene were present, pain returned more or less quickly after the limb was removed from the apparatus, as indicated in protocol 1 and table 3. Eventually amputation was performed in all four patients with frank gangrene (table 4). Three of this group were treated only a few hours, the totals ranging from 2 to 11 hours. The fourth patient was treated for a

TABLE III

Prolonged Effects of Suction and Pressure on Pain of Vascular Type

A. With frank gangrene or large, sloughing ulcer.
Patient 1. Temporary relief (only 6 hours' treatment). Amputation of arm.
2. Little, if any, relief (only 3 hours' treatment). Amputation of leg.
3. Conspicuous, but temporary, relief. Amputation of toe. Suction and pressure required to heal indolent, painful ulcer at site of amputation.
4. Conspicuous, but temporary, relief. Central slough enlarged slowly. Amputation of leg.

B. With indolent or slowly enlarging ulcers, and minor slough.
Patient 1. Almost complete relief.
2. Complete relief.
3. Complete relief.
4. Complete relief.
5. Almost complete relief.
6. Complete relief.
7. Complete relief.

C. With intermittent claudication both with and without ulceration.
Patient 1. Originally walked ¼ block. Stopped at 2 blocks by untreated leg.
2. Originally walked ½ block. Increased to 10–12 blocks.
3. Originally walked ¾ block. Increased to 1 block.
4. Originally walked ½ block. Increased to 2 blocks.
5. Originally walked ¼ block. No effect (only 3 hours' treatment).
6. Originally walked 1½ blocks. Increased to 10–12 blocks.

TABLE IV

Effects of Suction and Pressure on the Healing of Indolent or Enlarging Ulcers Associated with Peripheral Vascular Disease

I. Patients with local gangrene

Diagnosis	Size of ulcer	Course	Effect
1. Thromboangiitis obliterans	Gangrenous slough 5 × 6 cm.	Acute	None
2. Thromboangiitis obliterans	Gangrenous area 1 × 2 cm.	Acute	None
3. Arteriosclerosis	2.5 × 2.2 cm. Large central slough	Acute	Temporary

II. Patients with ulcers but without frank gangrene

1. Thromboangiitis obliterans	1.0 × 1.5 cm.	(Indolent-1 month)	Healed
2. Arteriosclerosis	1.0 × 0.9 cm.	(Acute)	Healed
	0.7 × 0.8 cm.		Healed
3. Arteriosclerosis, diabetes	2.0 × 1.1 cm.	(Indolent-3 months)	Healing
4. Arteriosclerosis	1.2 × 1.4 cm.	(Indolent-4 months)	Healed
	1.0 × 3.0 cm.		Healed
5. Thromboangiitis obliterans	1.0 × 1.2 cm.	(Enlarging)	Healed
6. Thromboangiitis obliterans	0.8 × 1.0 cm.	(Indolent-3½ months)	Healed
7. Thromboangiitis obliterans	0.8 × 0.9 cm.	(Indolent-5 months)	Healed

total of approximately 50 hours with conspicuous, but only temporary, relief; amputation was eventually necessary.

Patients with indolent or slowly enlarging ulcers, but without frank gangrene, large sloughs or extending necrosis, often obtained striking relief from rest pain. Sleep ordinarily became possible without sedatives after a few days. The results in patients with intermittent claudication were difficult to estimate and have been less striking, though in general slow improvement was observed. The subjective nature of the symptoms and the possibility of spontaneous recovery make it advisable to reserve judgment.

The diminished blood flow of peripheral vascular disease leads eventually to local gangrene, or to indolent ulceration which is resistant to treatment. Patients with frank gangrene did not improve significantly during or after exposure to pressure variations (table 4). One patient with a large sloughing ulcer under the malleolus showed temporary improvement, but very slow extension of the slough and continued pain made amputation eventually necessary. Those patients who had indolent ulcers without frank gangrene were markedly improved. The ulcers had, in some instances, been indolent or enlarging under treatment with antiseptics and heat for periods of several

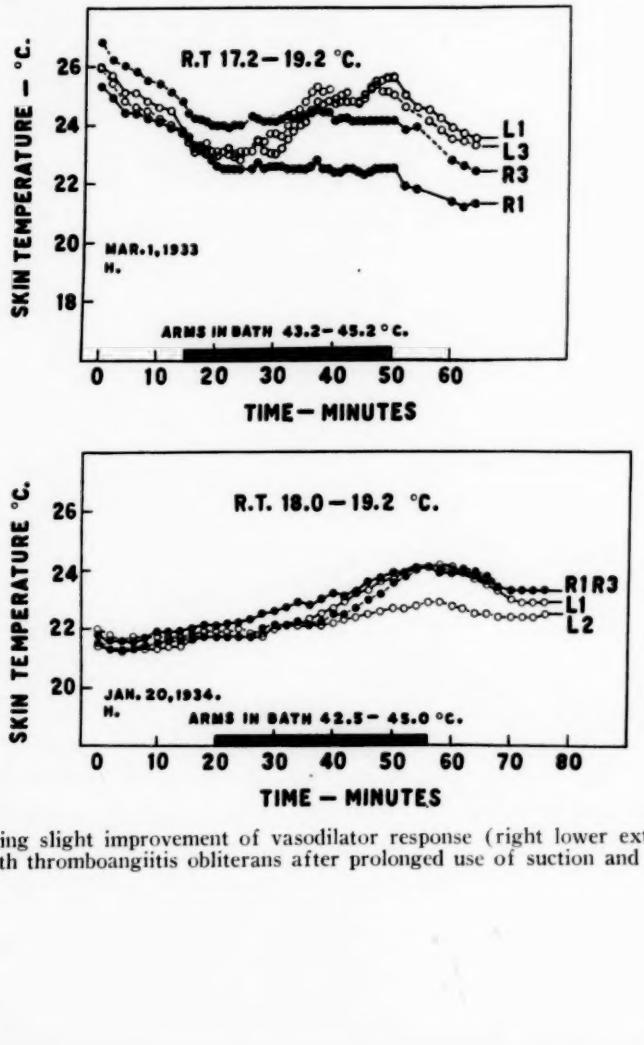

FIG. 7. Showing slight improvement of vasodilator response (right lower extremity) in a patient with thromboangiitis obliterans after prolonged use of suction and pressure.

months before pressure variations were used. The healing, which occurred during application of suction and pressure, was accompanied by improvement of skin color and diminution of rest pain.

The rise in skin temperature, the improvement of skin color, the diminution of rest pain and the healing of previously indolent ulcers indicate that alternate suction and pressure increases blood flow at least temporarily. At the present time it is impossible to do more than speculate upon the permanence of this improvement. Complete and lasting recovery depends upon the development of adequate collateral circulation. Sufficient time has not elapsed to determine to what extent increased blood flow depends upon the continued use of pressure variations.

In some patients collateral circulation develops slowly during and after treatment. Figure 7 illustrates observations on a patient in whom no response was observed during March 1933 in the right lower extremity. After the use of suction and pressure the right extremity showed during January 1934 a slight, but definite, increase in temperature during the immersion of forearms in warm water. The untreated extremity, on the contrary, exhibited on the second examination less vasodilator response than before. The patient illustrated in figure 8 showed no change in vasodilator response between February 1932 and March 1934 although considerable treatment was given during late 1933 and early 1934. Clinical improvement was distinct, however; rest pain and cyanosis disappeared almost completely, and an indolent ulceration following amputation healed without incident during the use of negative and positive pressure. The patient is at present ambulatory and able to work.

From the results summarized above it may be concluded that alternate suction and pressure increase blood flow temporarily, even after organic vascular disease has diminished, or abolished, vasodilatation. The changes of skin color, the alleviation of rest pain, the accelerated healing of indolent ulcers amplify the earlier evidence based on studies of skin temperature.[5, 6] Concerning the real therapeutic value of this procedure little can be said until a large series of carefully controlled and extensive clinical observations have been made. Reid and Herrmann have described the development of collateral circulation in patients with peripheral vascular disease after prolonged treatment by means of pressure variations in cycles of five minutes. They utilized at first [8] Bier's method in which negative pressure was applied very gradually for two minutes, maintained at —70 mm. Hg for one minute and then gradually relieved during two minutes, no positive pressure being used. More recently they [9] have adopted a procedure involving briefer periods of negative pressure alternating with positive pressure in cycles as short as 15 seconds.

Contraindications to the use of suction and pressure can be given at this time on theoretical grounds only. Active or acute infection may well be unfavorably influenced by the procedure. Osteomyelitis, however slight, makes it unlikely that complete healing of cutaneous lesions can be obtained

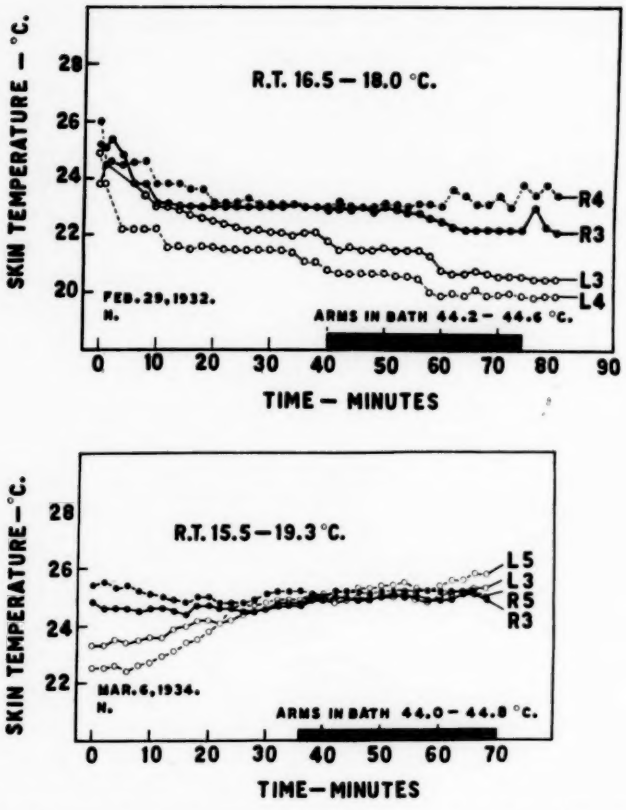

FIG. 8. Showing no change in vasodilator response of patient with thromboangiitis obliterans (subacute type) after the use of suction and pressure. Pain and cyanosis were much improved but blood flow was not sufficiently affected to change skin temperature when vasoconstrictor tone was diminished.

as long as drainage from beneath continues. When large masses of tissue are actually gangrenous, or sloughing, only temporary relief has so far been observed.

SUMMARY

It is necessary to detect beginning organic obstruction as early in the course of peripheral vascular disease as possible, since the therapeutic measures available depend to a large degree upon the ability of the blood vessels to dilate. Unfortunately, many patients reach the hospital after peripheral vascular disease has advanced to the stage when the arteries are no longer able to increase their diameter, though vasoconstrictor tone is entirely abolished. Even under these unfavorable conditions, however, it is still possible to increase blood flow by means of alternate suction and pressure. This procedure elevates skin temperature conspicuously, tends to relieve cyanosis, diminishes rest pain, and favors, at least temporarily,

the healing of superficial, indolent ulceration. Whether or not the development of collateral circulation can be so stimulated as to return tissue nutrition permanently to a normal state is not yet certain. The practical importance of suction and pressure in the treatment of peripheral vascular disease will necessarily depend to a great extent on the degree to which collateral vessels take over the function of those arteries which are closed by disease. There are indications that even if the patient can only be aided temporarily over crises of rest pain or ulceration, time will be gained for the natural development of collateral circulation so that a certain number of mutilating operations can be avoided.

REFERENCES

1. Gibbon, J. H., Jr., and Landis, E. M.: Vasodilatation in lower extremities in response to immersing forearms in warm water, Jr. Clin. Invest., 1932, xi, 1019–1036.
2. Landis, E. M., and Gibbon, J. H., Jr.: Simple method of producing vasodilatation in lower extremities, with reference to its usefulness in studies of peripheral vascular disease, Arch. Int. Med., 1933, lii, 785–808.
3. Scott, W. J. M., and Morton, J. J.: Differentiation of peripheral arterial spasm and occlusion in ambulatory patients, Jr. Am. Med. Assoc., 1931, xcvii, 1212–1215.
4. Landis, E. M.: The capillary pressure in frog mesentery as determined by micro-injection methods, Am. Jr. Physiol., 1925–1926, lxxv, 548–570.
5. Landis, E. M., and Gibbon, J. H., Jr.: Effects of alternate suction and pressure on circulation in lower extremities, Proc. Soc. Exper. Biol. and Med., 1933, xxx, 593–595.
6. Landis, E. M., and Gibbon, J. H., Jr.: Effects of alternate suction and pressure on blood flow to lower extremities, Jr. Clin. Invest., 1933, xii, 925–961.
7. Lewis, T.: Standard colors for use in study of vascular reactions of human skin, Heart, 1929, xv, 1–3.
8. Reid, M. R., and Herrmann, L. G.: Treatment of obliterative vascular diseases by means of intermittent negative pressure environment, Jr. Med., 1933, xiv, 200–204.
9. Herrmann, L. G., and Reid, M. R.: Pavaex (passive vascular exercise) treatment of obliterative arterial diseases of extremities, Jr. Med., 1933, xiv, 524–529.

THE ETIOLOGY OF ARTERIAL HYPERTENSION *

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The two questions most frequently asked of investigators engaged in the study of arterial hypertension are: (1) how do you treat patients with arterial hypertension; and (2) what is the cause of arterial hypertension? The answers to these closely related questions are always given with embarrassment and humility. The answer to the first question is relatively simple, for there are but few therapeutic measures the beneficial nature of which is proved to be specific. The answer to the second question, which I intend to consider here, is difficult and at best incomplete.

Extensive and reliable experimental data are available indicating that arterial hypertension may be induced in animals in several ways. In addition, observations on patients with arterial hypertension have disclosed numerous alterations in the physiological and chemical functions. It is because of the many possible ways of inducing experimental hypertension, and because of the numerous deviations in bodily functions associated with hypertension, that the study of the etiology of *clinical* hypertension is so difficult. What we desire to know is the cause of arterial hypertension as it exists *in man*. The fallacies most frequently encountered in the solution of this problem are: (1) generalizations from experimental observations in animals, without proper appreciation of the clinical problems; (2) an inadequate clinical study of the patient as to the type of arterial hypertension and as to its secondary complications; (3) the frequent misinterpretation of a finding which coincides with or is the result, rather than the cause, of arterial hypertension; (4) the inaccuracy of the methods applied.

Data bearing on the etiology of arterial hypertension have accumulated so rapidly during recent years that unless one has had experience in investigating the varied aspects of the problem one is completely lost in the maze of data. With a full realization that the problem is far from being settled, I shall present a viewpoint based on a critical analysis of the literature and on some personal experience.

The main lines of approach to the problem may be divided into the following groups: (1) the rôle of circulating substances, including hormones; (2) the influence of the nervous system; (3) the reactivity of the vascular system and mechanical factors; (4) infections and allergy; and (5) constitutional factors.

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1. The Rôle of Circulating Chemical Substances in Arterial Hypertension

This approach to the etiology of hypertension is perhaps the most obvious, particularly since examples of hormones with a vasoconstrictor effect are available. The search for chemical substances in the blood and in the urine actually goes back to the first clinical concepts of nephritis established by Bright and Johnson. It would be useless to enumerate here investigations of all the substances held responsible for the development of arterial hypertension. It is clear from the literature that glucose, salt, purine and protein substances are not etiological agents. Among the chemical theories which have interested investigators in recent years, there are several of particular interest:

Guanidine. The first is that of Major [2, 3, 4] who proposed that retention of guanidine bases is responsible for essential hypertension. In support of his assertion he has demonstrated that administration of certain guanidine compounds produces a rise in the blood pressure of experimental animals; and has claimed that in patients with essential hypertension the excretion of guanidine bases in the urine is diminished, and the guanidine content of the blood increased. Major's contention cannot be considered valid at present (1) because the amounts of guanidine compounds administered to animals are relatively large, and (2) particularly because the reliability of the chemical methods which he used for the demonstration of guanidine bases in the blood and urine is questionable.[5, 6] Kleeberg,[7] using a colorimetric method similar to that used by Major, has observed an elevation of the guanidine content of the blood in patients without hypertension. In patients with hypertension, he found that the guanidine content was elevated only when there was an accumulation of protein derivatives and products of intestinal putrefaction; in a number of cases he observed normal colorimetric values. Turriès and Robert [8] and likewise Jackson [9] in our clinic were unable to establish a correlation between hypertension and the guanidine content of the blood. It should be remembered that more recent experiences with creatinine and urea clearance tests indicated that an impaired excretion of some compounds may occur in patients with hypertension without necessarily bearing on the etiology of the condition.

Cholesterol. Schmidtmann [10] has observed a temporary elevation of the blood pressure in rabbits following prolonged cholesterol feeding. Westphal,[11] on feeding rabbits a high cholesterol diet, observed that their blood pressure rose concomitantly with an increase in the serum cholesterol. Investigating a series of 80 cases of essential hypertension, he also found that the cholesterol level was above the normal range in 71 per cent of the cases. Weil and Guillaumin [12] and Askanazy [13] found high cholesterol values in the plasma of patients with hypertension. Thus, on the basis of observations on man as well as of experiments on animals, Westphal and others consider cholesterol as one factor in the genesis of essential hyper-

tension. Although the experimental work of Schönheimer,[14] Shapiro[15] and Thölldte,[16] and the chemical studies in man of Mjassnikow,[17] Loewenstein,[18] Harris and Lipkin[19] have shed much doubt on the rôle of cholesterol in the production of arterial hypertension, we[20] reinvestigated this problem in 75 cases of hypertension. Our study revealed that patients with secondary renal complications were more apt to show hypercholesteremia than were those with secondary cardiac involvement. On the other hand, of 37 patients with uncomplicated hypertension, only five showed an unexplained hypercholesteremia. We have therefore concluded that the elevation of cholesterol is the result, rather than the cause, of changes in the cardiovascular system in arterial hypertension.

Potassium-Calcium Ratio. Since experimental observations[21, 22, 23, 24] suggest that changes in sympathetic-parasympathetic and potassium-calcium balance can be detected by their effect on the action of hormones, Kylin[25] investigated the relation between the reaction to epinephrine and the potassium-calcium ratio. He observed that in cases with a potassium-calcium ratio of from 0.7 to 2.15, which is within his normal range, there were normal reactions to epinephrine. The blood pressure curve of patients with essential hypertension having a ratio over 2.15 was consistently vagotonic; that is, the patients exhibited a fall in blood pressure after epinephrine. Kylin,[25] Brems[26] and Loewenstein[18] found a definite rise in potassium content in cases of essential hypertension, while calcium values were either at, or below, the lower limits of normal. Jansen[27] found that in patients with arterial hypertension, with or without renal involvement but without cardiac failure, the calcium values were at the lower level of the normal range. Stieglitz[28] investigated 47 cases of pregnancy, with arterial hypertension as a secondary complication. He found that the average calcium value in his pregnant patients coincided with that in his controls, and therefore he concluded that hypocalcemia is not a factor in the hypertension of pregnancy. We[20] have reinvestigated the significance of the potassium-calcium ratio and the inorganic phosphorus, with the aid of recently devised exact methods, in 75 cases of hypertension and in 25 control cases. The potassium and calcium content of the blood in patients with uncomplicated hypertension was normal. In patients with cardiac complications the potassium content was somewhat high. We were unable to find any correlation between the potassium-calcium ratio of the blood and hypertension. Elevation of the ratio, when present, was the result of circulatory failure.

Peptones. Hülse and Strauss[29] of the Volhard Clinic have claimed that peptone-like substances in the blood of patients with hypertension caused by glomerulonephritis and eclampsia are responsible for hypertension, inasmuch as these circulating substances sensitize the effect of circulating epinephrine, causing vasoconstriction. This problem was again investigated at the Boston City Hospital by Jackson[30] who, after devising an accurate method for the determination of peptones in the blood, failed to observe any elevation in patients with hypertension.

Epinephrine and Pituitrin. While the aforementioned chemical theories are related to substances which can be determined chemically in the blood or the urine, the suggestion that circulating hormones, particularly epinephrine and pituitrin, are responsible for hypertension is supported by indirect evidence only. Ever since the discovery by Oliver and Schäfer [31] of the pressor effect of extracts of the medulla of the suprarenal gland, it has been suggested by Vaquez [32] and other clinicians [33, 34, 35, 36] that hyperadrenalemia is responsible for at least a certain type of hypertension. These suggestions, however, are not supported by the demonstration of an increased epinephrine content of the blood. While earlier investigators have claimed to demonstrate such an increase with biologic tests, their observations have remained unconfirmed even when such sensitive tests were applied as were claimed to give a positive reaction in a 1:700,000,000 dilution.[37] The comparative analysis of the adrenal gland for epinephrine also failed to yield convincing evidence that the epinephrine content of the gland from patients with hypertension differs from that in normal subjects.[38, 39] Hence the only tangible evidence in favor of the epinephrine origin of hypertension is the apparent correlation between certain hyperplasias and tumors of the adrenal gland, and arterial hypertension. It should be remembered, however, that hyperplasia and adenoma of the cortex are frequently not associated with hypertension, but these frequent negative findings in postmortem examinations are not reported. Furthermore, no evidence exists that the cortical tissues of the adrenal gland contain vasoconstrictor substance. There are reported in the literature a few cases of tumors of the adrenal gland, partly of medullary and partly of cortical origin, which were associated with hypertension of severe and at times widely fluctuating course.[40, 41, 42] Whether the cause of arterial hypertension in these rare instances was epinephrine, or whether the tumor and the hypertension were coincidental parts of a constitutional make-up, or, finally, whether the tumor induced certain changes in the bodily structure which then indirectly caused arterial hypertension, cannot be determined from the available evidence.

The *pituitary theory* as to the origin of certain types of hypertension has aroused much interest recently, mainly through the contributions of Anselmino [43, 44] and Cushing.[45, 46, 47, 48] Anselmino and Hoffmann have claimed to demonstrate that the blood and urine of women with eclampsia and arterial hypertension contain increased amounts of a substance which exerts a vasopressor and an anti-diuretic effect. These investigators have claimed that the substance is pituitrin. Recently, however, Hurwitz and Bullock [49] at the Boston Lying-In Hospital, and Page [50] at the Rockefeller Institute were unable to confirm the observations of Anselmino. In describing the syndrome of basophilic adenoma, Cushing [47] has called attention to the fact that arterial hypertension is frequently present. In support of his theory of the pituitary origin of hypertension he cites the work of Anselmino [43, 44] and the observation of increased basophilic cells of the anterior lobe in the presence of hypertension.[51, 52, 53] Since two groups of

investigators have failed to confirm the work of Anselmino, and since the significance of increased basophilic cells in general, and their presence in hypertension in particular, is not clear, Cushing's theory on the etiology of hypertension still lacks adequate evidence. In view of the association of basophilic adenoma with bodily changes involving different types of tissues, the interrelation between basophilic adenoma and hypertension is open to a number of other explanations than the effect of circulating pituitrin.

Increased *thyroid secretion* has also been held responsible for arterial hypertension,[54, 55] but an examination of the data fails to reveal any direct relationship between hyperthyroidism and true arterial hypertension.

Vasoconstrictor Substances of Undetermined Nature. If epinephrine, pituitrin or other substances with a vasoconstrictor effect are responsible for the development of arterial hypertension, obviously one would expect to be able to demonstrate an increased vasoconstrictor effect induced by concentrated extracts of the blood and urine. A series of such investigations has been conducted mainly by the Volhard school in recent years. Bohn and his associates [56, 57, 58, 59] claim that extracts of the blood and urine of patients with the so-called "pale hypertension" of Volhard, which includes cases with glomerulonephritis, malignant hypertension and eclampsia, exert a marked constrictor effect on the vascular systems of rabbits and cats. Marx [60] has observed similar responses in unanesthetized dogs following the injection of extract of blood from a group of patients. Although we do not entirely agree with the rationale of Volhard's rigid classification of "pale" and "red" hypertension, nevertheless Capps, Ferris, Taylor and I [61] have reinvestigated the problem of circulating vasopressor substances in the blood and particularly in the urine. We were able to demonstrate a pressor substance in the blood and in the urine in normal subjects, as well as in patients with hypertension. This vasopressor substance, however, has no relation to the degree or to the type of hypertension. In our studies, the most powerful vasopressor substances were extracted from the urine of normal subjects. It is interesting that the available evidence indicates that this *vasopressor substance* acts on the vasomotor centers and that its effect depends on the state of these centers. The work of Bohn and Marx has also been disproved recently by de Wesselow [62] and Page.[50]

Alcohol and Tobacco. Among the exogenous chemical factors, alcohol and also tobacco have been held responsible for the development of hypertension. Without giving a detailed analysis of the literature [63] one may conclude that both pharmacologic and clinical evidence is lacking to support the claim that alcohol is responsible in any manner for arterial hypertension. Similarly, no convincing data are available on the etiologic influence of tobacco.[64] Although evidence is available indicating that tobacco and nicotine can induce elevation of the blood pressure in animals,[65, 66] and that patients with arterial hypertension may exhibit accentuation of the elevation of the blood pressure during a period of excessive smoking, there are no data indicating that nicotine plays a rôle in the causation of hypertension.

The fact that a statistical analysis of the sex incidence in a large group of cases of essential hypertension at the Boston City Hospital [67] revealed a greater frequency among females may also be used as indirect evidence against the significance of alcohol and tobacco in hypertension.

Lead. There is only fair evidence that lead is responsible in some instances for the development of arterial hypertension. Pharmacologic studies and clinical observation reveal clearly that lead compounds exert a constrictor effect on smooth muscles.[68, 69] Temporary hypertension in acute poisoning, particularly during lead encephalopathy, is frequently observed. That patients who suffer from chronic lead poisoning exhibit an increased incidence of sclerosis of the arterial vessels and elevation of the blood pressure is also suggestive. The development of this true, persistent hypertension is due to a sclerosis of the vascular system.[70, 71, 72] Obviously, however, lead explains but a small fraction of the cases of hypertension.

Thus, to summarize the results of investigators of more than two decades, while a priori the theory of the etiologic rôle of circulating vasoconstrictor substances seems plausible, actually extensive experimental and clinical studies fail to support such a contention. Lead is probably responsible for a few instances of hypertension. The correlation between certain tumors of the adrenal and pituitary glands and hypertension is suggestive, but the nature of this correlation is not known. Constitutional rather than direct hypersecretory functions are probably active. While this negative conclusion may appear to be discouraging, actually it is constructive for it allows us now to turn our attention more definitely toward other possibilities.

2. The Rôle of the Nervous System in the Causation of Hypertension

The significant rôle of the nervous mechanism in the regulation of blood pressure is well known. Although recent years have seen important progress in the field of the chemical regulation of the circulation, as well as in the field of neurochemical interrelations, today the dominant rôle of the nervous system in the regulation of blood pressure stands out even more definitely. In this nervous regulation, the sympathetic vasomotor system with its constrictor influence is a primary factor, its effect being partially inhibited by the parasympathetic vasomotor nervous system, particularly through the carotid sinus and the aortic depressor reflexes.[73, 74, 75] Elevation of the blood pressure results through a shift of the sympathetic-parasympathetic vasomotor nervous balance owing either to decreased function of the depressor (parasympathetic) reflexes, or to increased activity of the pressor (sympathetic) reflexes. That experimental elimination of the depressor reflexes actually induces arterial hypertension has been shown recently.[74, 76]

It has been suggested, therefore, that *hypoactivity of the carotid sinus and other depressor reflexes* is responsible for arterial hypertension. This

suggestion, however, based on animal experimentation, is not supported by clinical studies. If hypoactivity of the carotid sinus reflex is responsible for the development of arterial hypertension, one would expect the depressor response to be reduced or absent following stimulation of the sinus. Such is not the case in our experience, for mechanical stimulation of the sinus of patients with hypertension resulted in a relatively increased rather than in a decreased depressor response.[77] It may be contended, however, that although mechanical stimulation of the carotid sinus induces a hyperactive response under physiologic conditions, atheromatous changes in the sinuses and in the aorta may interfere with transmission of the intravascular pressure to the sensory nerve endings. Under such conditions the nerve endings may continue to respond to direct external mechanical stimulation, and yet intrasinal pressure changes would result in but slight or no reflex response. Such a suggestion of Hering[73] can be rejected on the basis of the careful histologic studies of Sunder-Plassmann,[78] who observed a lack of correlation between atheromatous changes in the sinus and degeneration of the nerve endings. Von Hasselbach,[79] and recently Keele,[80] found no correlation between the degree of structural change in the sinus and the aorta and the blood pressure level. In a clinical examination of the structural characteristics of the sinuses we have had similar results.[77, 81] One may therefore conclude that studies on man do not favor the contention that hypofunction of the carotid sinus or aortic depressor reflexes is responsible for arterial hypertension. One should realize, on the other hand, that the rôle of decreased depressor reflexes requires further study.

The second possibility, namely, that an *increased pressor nervous mechanism* is responsible for arterial hypertension, is based on fair evidence. The fact that a constriction of the arteriolar system exists in hypertension is generally accepted.[82, 83, 84] This narrowing of the arteriolar system is present in hypertension of different types, although the extent and the organ distribution may vary in the same as well as in different types of hypertension. If narrowing of the arteriolar system results from constriction of the smooth muscles, it is obviously due to increased tonus of the sympathetic system. The sympathetic system is the constrictor and the dominant portion of the vasomotor nervous system; hence variations in its tonus are to be expected. From a comparative study of a group of patients with essential hypertension and a control group, we[85] have concluded that, on the whole, the influence of the sympathetic nervous system was more pronounced and that of the parasympathetic less so in patients with hypertension than in control subjects with normal cardiovascular systems. This increased sympathetic balance was a statistical conclusion and was not present in every case. The question now arises as to the cause of this increased tonus of the sympathetic nervous system. To state, as von Monakow[86] has done, that the vasomotor center is " set " on a higher level in hypertension, is not particularly constructive in the further analysis of the problem. Bordley and Baker[87] have claimed that ischemia resulting from arteriosclerosis of the medullary

centers is a factor. Cutler's [88] more recent study, as well as routine experiences, throws much doubt on the general rôle of medullary arteriosclerosis. That this factor, as well as local circulatory disturbances from pressure caused by tumors or other intracranial pathology, may play a rôle in rare instances, seems very plausible. Studying the cerebral circulation of patients with essential hypertension, Raab [89] in our laboratory has observed an increased oxygen difference indicating a slower blood flow through the brain. He has interpreted this finding as indicating ischemia of the cerebral circulation in hypertension. In view of the ages of the patients studied, as well as of the presence of arteriosclerosis, and because our later experience has demonstrated a more severe degree of cerebral ischemia in a number of conditions unassociated with hypertension, we cannot agree with Raab's conclusions. The ischemic etiology of the hypertonus of the vasomotor center cannot be accepted at present as the cause of hypertension.

Because patients with essential hypertension often exhibit an accentuation of the elevation of the blood pressure under *emotional stress,* and a fall during relaxation, the emotional etiology of hypertension has also received much attention. On careful examination, however, this theory does not seem to be so obvious as on first inspection. Dramatic examples of elevation of the blood pressure under stress and its fall to normal during relaxation are not lacking. Statements that patients with hypertension present a high-strung, driving personality and that hypertension is a condition of our modern age of wear and tear are also numerous in the literature.[90, 91] Whether vascular diseases with arterial hypertension are really modern diseases is quite doubtful. Apoplexy, heart failure of nonvalvular origin, and uremia have always been common clinical manifestations. Hypertension occurs frequently among the population of quiet, farming villages. The rôle of emotions in hypertension is not so evident in hyposensitive races as in hypersensitive and rather excitable races. Careful analytical study of the psychic make-up of hypertensive patients, including control observations, is still lacking. The difficulty of the problem is further increased by the fact that frequently during elevation of the blood pressure, changes in personality appear which are secondary to the elevation of the blood pressure.[92] In a comparative analysis of a group of patients with essential hypertension and with normal cardiovascular systems, overexcitability, impulsiveness and a tendency to worry was, nevertheless, more frequently present in the hypertensive group.[85] In a study of 1090 ambulatory patients with essential hypertension, we [93] have observed a symptomatology quite similar to that in patients with neurosis. This was also found by Davis [94] and by Ayman and Pratt.[95] We [93] have pointed out, however, that a large control group of patients with obesity and with psychoneurosis, but with normal blood pressure, exhibited the same symptomatology as patients with arterial hypertension. Thus, although psychic trauma and conflicts, as well as abnormal sensitivity of the psyche, play a rôle in essential hypertension, personality and emotional factors *alone* are not adequate in the

explanation of even a single type of hypertension. This contention is also supported by the fact that emotional disturbances in psychoses bear no relationship to the level of the blood pressure. It has been rightly emphasized by Dennig, Fischer and Beringer [96] that no close relationship exists between "cortical" and "autonomic" functions. If, on the other hand, in hypertension a closer interrelation exists between the psychic factor and the sympathetic centers, this requires further explanation.

In addition to the suggestive central origin of essential hypertension, it is possible that pressor reflexes play an important rôle in hypertension associated with primary genito-urinary pathology.

3. The Reactivity of the Vascular System and Mechanical Factors

As has been pointed out, an increased resistance of the arteriolar bed caused by a narrowed arteriolar system is one of the main features of the bodily state in hypertension. Such a generalized change in the arteriolar resistance is satisfactory explanation for the development of the majority of types of hypertension. One mechanism in the development of a narrowed arteriolar system, namely, increased nervous tonus, has already been discussed. A second possibility, namely, a primary cellular or mechanical origin, also merits careful consideration.

An increased constrictor response of the minute vessels to local heat and mechanical stimuli has been observed in patients with essential hypertension both by Lange [97] and in our laboratory.[85] Although we do not at present possess data on the total transectional area of the arteriolar system, clinical and postmortem experiences reveal variations in the arterial lumen in different subjects. At times the narrowed state of the vascular system of women in good health, who later develop hypertension during pregnancy, is striking. It is also established that with advancing age there is progressive accumulation of intercellular cement substances, loss of elasticity of tissues, arteriosclerotic and other involutionary changes which are all included in the collective term of "changes of senescence." These changes result in the shrinkage of the lumen of the small arterial vessels and in a secondary progressive rise in blood pressure. A moderate degree of progressive rise is thus an expression of physiologic senescence. In persons with congenitally hypoplastic arterial systems, however, the normal changes of senescence result in a marked increase in the vascular resistance. In persons with increased severity of degenerative changes an increased arteriolar resistance also develops. That mechanical factors of increased peripheral resistance play a rôle in arterial hypertension is demonstrated by cases of coarctation of the aorta, in which elevation of the blood pressure exists in vascular areas originating from portions of the aorta in front of the resistance; and by cases of obesity in which the hypertension may completely disappear with reduction of body weight. The fact that a sudden rise in

the incidence of hypertension coincides with the age of onset of involutionary changes of the body in each sex, also supports this view.[67] Thus in a study of the age distribution of 1620 ambulatory patients with hypertension, the bulk of the cases were noted after the age of 40, coinciding with the onset of involutionary changes, such as climacteric, and not in youth when the sensitivity of the nervous system is greatest and when mild, temporary emotional hypertension is relatively common.[98, 99] The finer mechanism through which a primary generalized increased arteriolar resistance of nervous, cellular or other origin results in an increased cardiac force and hence in hypertension, is not clear. It has been suggested that with the increased arteriolar resistance as the result of local ischemia, tissue metabolites stimulate efferent nerve endings of a widespread cardiopressor reflex.[100]

It has also been claimed recently that in certain types of essential hypertension, in addition to changes in the minute vessels there is a progressive loss of elasticity and of the propulsive action of the aorta and other large vessels.[101, 102, 103] The decreased elasticity of these large arteries also explains the relatively high systolic pressure and the high pulse pressure without increased cardiac output which were observed by us recently.[81] This pertinent problem, particularly as to whether changes in the arteries occur early or only in the later stage, merits further investigation.

The mechanical theory that hypertension of nephritis is due to local vascular resistance of the kidneys, first proposed by Traube,[104] is not tenable, both because of theoretical objections and because our studies of the hemodynamics of the circulation in hypertension of nephritic origin reveal a widespread vasoconstriction.[83] That local disturbance of the renal circulation can induce experimental hypertension, on the other hand, has been shown repeatedly. Such an experimental hypertension has been induced by excising varying amounts of kidney tissue,[105, 106, 107, 108, 109] by damaging the kidney with roentgen-rays,[110] by local renal venous stasis,[111, 112, 113] and recently by progressive clamping of the renal arteries.[114] Fahr [115] maintains that renal ischemia plays a rôle in the induction of hypertension associated with nephrosclerosis. There are, indeed, a number of clinical examples indicating that local diseases of the genito-urinary tract are followed by arterial hypertension. The explanation of hypertension of kidney and genito-urinary system origin does not lie in increased local vascular resistance but, as has been pointed out recently by Goldblatt, Lynch, Hanzal and Summerville,[114] is based on one or more of the following possibilities: (a) afferent impulses are set up from the affected nerve endings in the ischemic kidneys to the vasomotor centers, whence a general vasoconstriction is induced; (b) afferent impulses from the ischemic kidney may influence some internal secretory gland; and (c) there may be an accumulation or new formation of some substance or substances which, after entering the blood stream, induce a general vasoconstriction. At present the exact mechanism of hypertension induced from the kidney and urinary passages is not known.

4. The Rôle of Infections and Vascular Allergy

Evidence that infections play a direct etiologic rôle in the *majority* of instances of hypertension is lacking. Clinical observations, on the other hand, furnish ample evidence indicating an indirect etiologic rôle for infections. There is not a single type of infectious agent which is regularly associated with hypertension. The majority of infections associated with hypertension first produce kidney lesions, and hypertension then develops as a secondary manifestation. In this sense, streptococci are indirectly responsible for certain cases of hypertension. Similarly, urinary infections of childhood with pyelonephritis, or with partial stricture of the ureter, cause hypertension, which at times imitates the clinical picture of essential hypertension. The hypertension of mitral stenosis [116] also represents such an indirect relationship. The apparent relationship between syphilitic aortitis and hypertension [117] can be explained by changes in the aorta and particularly by narrowing of the lumen of arterial openings.

The claim that allergy plays a rôle in arterial hypertension [118, 119] cannot be accepted as yet. In certain cases of malignant hypertension, particularly in periarteritis nodosa, infections such as peridental abscess, pyelitis, perinephritic abscess, seem to play an indirect rôle. The problem of vascular allergy has not been investigated with the care it deserves.

5. Constitution and Arterial Hypertension

In the foregoing discussion we have concluded that vascular changes of senescence, local irritability of the vascular tissues, psychic factors, increased tonus of the autonomic nervous system, increased pressor reflexes, infections and lead play a rôle in the development of various types of arterial hypertension. It should be emphasized, however, that any of these factors may be present in even greater intensity in persons with normal blood pressure. Thus, although the rôle of the above factors stands out clearly, their relation to hypertension is not a direct and consistent one. The postulation, therefore, of an added factor seems inevitable. One may state with justification that these etiologic agents result in hypertension only if they act on persons with a certain psychophysical make-up. The fact that extensive investigations have failed to reveal any single factor which regularly causes arterial hypertension, strengthens the importance of the rôle of the constitution.

Detailed knowledge of this constitution is still lacking. It is probable that the physical aspect of the body habitus is the least important. Weitz,[120, 121] de Nádor-Nikitits [122] and others deny that the sthenic habitus (megalosplanchnic habitus of Viola or pyknic of Kretschmer) has a special relation to hypertension. Daily clinical experience, also, suggests that among patients with pronounced hypertension all types of bodily habitus occur with approximately the same frequency. It is suggestive, then, that an understanding of the inherited anatomic and functional characteristics of the nervous and

vascular systems rather than the bodily habitus will eventually bring the solution. It is known that the vascular and nervous systems are particularly apt to transmit constitutional stigmata. Striking examples of a hereditary history in hypertension, nephritis, and cerebral vascular accidents have been known to clinicians ever since Forestus in the sixteenth century called attention to the hereditary occurrence of apoplexy.

O'Hare, Walker and Vickers [124] elicited a family history of vascular disease in 68 per cent of a group of patients with arterial hypertension. On the basis of an extensive study Weitz [120, 121] concluded that hypertension is inherited as a dominant characteristic. Recently Ayman [125] has presented additional data on the rôle of heredity. The fact that a hereditary history cannot be obtained in a higher percentage of cases is natural, and does not invalidate the significant rôle of the constitution; for a hereditary history is but partial and rather crude evidence of hereditary constitution, and just as the dividing line between what constitutes a normal person and one with hypertension is ill-defined, so is there no hard and fast division between the constitutional characteristics possessed by the two types.

Comment

In a consideration of the pathogenesis of hypertension, the general nature of the problem must be viewed as a whole. Just as before the discovery of insulin it was of aid in research to consider diabetes mellitus as a disease caused by disturbed function of the islands of Langerhans, and hence primarily a deficiency disease; so it is equally important to appreciate that arterial hypertension is not a disease entity but a bodily state of multiple etiology. We use the term "arterial hypertension" only because we can measure conveniently an important aspect of the circulation. The alteration in the blood pressure, however, is not the primary, nor even the most important, aspect of the problem. Change in the minute arterial vessels, which we cannot measure at present, is the primary site of the vascular change. Not only is the character of these vascular changes varied, but the same type of change, such as diffuse arteriolar spasm, is induced by different etiologic factors.

In taking the level of the blood pressure as an index of peripheral vascular changes, we have selected a circulatory function which undergoes considerable variation even in health, for in the homeostasis of the body arterial tension is not a rigid constant, when compared with body temperature and chemical regulation of the blood. Hence, we are quite arbitrary in considering a systolic pressure of 145 mm. Hg "normal" and a pressure of 155 "hypertension." The transition from a normal to hypertensive state is very gradual. In the majority of instances of hypertension we are dealing with but a moderate accentuation of the physiologic factors. Experience, on the other hand, has taught us that patients with markedly

elevated blood pressure frequently exhibit functional and structural disturbances of various organs; hence the clinical emphasis on the problem of hypertension is justified.

In spite of numerous investigations with negative results and faulty conclusions, the labor of the past two decades has resulted in remarkable progress in this important and difficult field. The fact that we have put suggestions and theories to the acid test of experimental research in itself represents a great advance. Much is known today of the hemodynamics and the vascular state in arterial hypertension. We have appreciably clarified the reversible interrelation between hypertension and kidney pathology. We have also definitely ruled out the suggestion that alterations in the cardiac output, stroke volume, blood volume, or viscosity of the blood are primary factors in the pathogenesis of the disease. On having established the significance of the stenotic state of the arteriolar system and of diminished elasticity of the larger arteries, today we are permitted to turn our efforts toward the primary etiologic mechanisms. Much is yet to be learned concerning this aspect of the problem. The fact, however, that extensive and painstaking search has failed to reveal any single factor of chemical or nervous nature which specifically and regularly induces hypertension seems to us very significant. It suggests that we may be dealing with a condition of multiple rather than of single etiology. Perhaps success in unfolding the nature of diseases of primary or of single etiology has wrongly trained us in the past half century to search always for a single cause of a disease.

From the above presentation it is clear that a number of factors definitely bear on the etiology of hypertension. It was emphasized that the factor or factors which are definitely active in a given case may not be present in all cases of the same type of hypertension; and furthermore the factors responsible in hypertension may occur in subjects with normal blood pressure. We wish to emphasize that this apparent contradiction does not obviate the rôle of these factors, but it suggests a special "affinity" or "susceptibility" on the part of the patient for these precipitating factors. Physiologic examples in human beings are numerous showing that an identical nervous or chemical stimulus exerts its effect on different organs in different groups of subjects.[126] Thus in the study of the etiology of arterial hypertension we should always analyze the primary constitutional characteristics of the patient, as well as the secondary precipitating factors. Today suggestive experimental and clinical evidence is available indicating that the rôle of inheritance and constitutional predisposition are represented mainly by inherited and at times acquired local irritability of the minute vessels, hyperirritability of the sympathetic vasomotor centers, and hypoplastic development of the vascular system. Among the secondary factors acting on such constitutionally susceptible nervous and vascular systems are emotional stress, physiologic changes of involution and senescence, obesity, certain types of infections, reflexes, particularly from the genito-urinary organs, and a few exogenous chemical substances. The relative rôle of

these factors varies considerably. The present evidence indicates that in the great majority of instances involutionary and senescent changes are active in the constitutionally predisposed individuals. The present classification of primary or essential (benign and malignant) and secondary hypertension of kidney origin indicates mainly the clinical and morphologic state of the body, but does not correspond to a single characteristic etiology.

The interpretation of hypertension as given here carries with it a certain amount of argument against the possible effectiveness of drugs, serologic or substitutional therapy. It implies that prevention and elimination of the secondary precipitating factors represent the main approach in treatment. While such a belief may seem pessimistic, since it eliminates at once the rationale of a search for a "cure," it is, nevertheless, in accordance with clinical experience, and furthermore emphasizes the rôle of physicians as advisors of patients rather than as dispensers of medication.

BIBLIOGRAPHY

1. Weiss, S.: Development of clinical concept of arterial hypertension, New Eng. Jr. Med., 1930, cii, 891–897.
2. Major, R. H.: The possible relationship between guanidine and high blood pressure, Am. Jr. Med. Sci., 1925, clxx, 228–232.
3. Major, R. H., and Weber, C. J.: Possible increase of guanidine in blood of certain persons with hypertension, Arch. Int. Med., 1927, xl, 891–899.
4. Major, R. H., and Weber, C. J.: Observations on depressor substances in certain tissue extracts, Jr. Pharmacol. and Exper. Therap., 1929, xxxvii, 367–378.
5. Greenwald, I.: Are guanidines present in urines of parathyroidectomized dogs? Jr. Biol. Chem., 1924, lix, 329–337.
6. White, F. D.: Nature of picrate obtained from normal urine by method of Findlay and Sharpe, Jr. Biol. Chem., 1927, lxxi, 419-427.
7. Kleeberg: Habilschr. 1929; Quoted by Volhard, F., and Suter, F.: Handbuch der inneren Medizin. Vol. IV. Nieren und ableitende Harnwege, 1931, Julius Springer, Berlin, p. 418.
8. Turriès, J., and Robert, S.: Récherches cliniques sur la guanidine du sang (en dehors de la tétanie), Presse méd., 1930, xxxviii, 85–86.
9. Jackson, H., Jr.: Unpublished study.
10. Schmidtmann, M.: Experimentelle Studien zur Pathogenese der Arteriosklerose, Virchow's Arch. f. path. Anat., 1922, ccxxxvii, 1–21.
11. Westphal, K.: Untersuchungen zur Frage der Entstehungsbedingungen des genuinen arteriellen Hochdruckes, Ztschr. f. klin. Med., 1924–25, ci, 558–670, 584.
12. Weil, M. P., and Guillaumin, C. O.: Hyperglycémie, hypercholéstérinémie augmentation des composés uriques globulaires et hypertension artérielle variable: son origine rénale, Ann. de méd., 1926, xix, 415–427.
13. Askanazy, S.: Rhodan-Kalzium-Diuretin gegen Hypertonie, München. med. Wchnschr., 1927, lxxiv, 1793–1794.
14. Schönheimer, R.: Über die experimentelle Cholesterinkrankheit der Kaninchen, Virchow's Arch. f. path. Anat., 1924, ccxlix, 1–42.
15. Shapiro, S.: Studies in atherosclerosis; relation of glands of internal secretion to its development, Med. Jr. and Rec., 1927, cxxvi, 284–287.
16. Thölldte, M.: Hypercholesterinämie, Blutdruck und Gefässveränderungen im Tierversuch, Beitr. z. path. Anat. u. z. allg. Path., 1927, lxxvii, 61–120.

17. MJASSNIKOW, A. L.: Klinische Beobachtungen über Cholesterinämie bei Arteriosklerose, Ztschr. f. klin. Med., 1925, cii, 65–78.
18. LOEWENSTEIN, W.: Chemische Blutbefunde bei der essentiellen Hypertension und ihre Bewertung, Ztschr. f. klin. Med., 1928, cvii, 52–60.
19. HARRIS, I., and LIPKIN, I. J.: High blood pressure and cholesterin, Brit. Med. Jr., 1930, i, 587–588.
20. WEINSTEIN, A. A., and WEISS, S.: Significance of potassium-calcium ratio and of inorganic phosphorus and cholesterol of blood serum in arterial hypertension, Arch. Int. Med., 1931, xlviii, 478–499.
21. VON KONSCHEGG, A.: Über Beziehungen zwischen Herzmittel- und physiologischer Kationenwirkung, Arch. f. exper. Path. u. Pharmakol., 1912–13, lxxi, 251–260.
22. ZONDEK, S. G.: Über die Bedeutung der Calcium- und Kaliumionen bei Giftwirkungen am Herzen, Arch. f. exper. Path. u. Pharmakol., 1920, lxxxvii, 342–355.
23. ZONDEK, H., and UCKO, H.: Die Zweiphasenwirkung der Hormone, Klin. Wchnschr., 1925, iv, 6.
24. KYLIN, E.: Von der Bedeutung der K-Ionen für die Insulinwirkung, Klin. Wchnschr., 1925, iv, 1455.
25. KYLIN, E.: Die Hypertoniekrankheiten, 1926, Julius Springer, Berlin.
26. BREMS, A.: Über den Kalium- und Calciumgehalt des Blutserums unter normalen und unter gewissen pathologischen Verhältnissen, Acta med. scandinav., 1927, lxvi, 473–483.
27. JANSEN, W. H.: Der Kalkgehalt des menschlichen Blutes unter pathologischen Verhältnissen, Deutsch. Arch. f. klin. Med., 1924, cxliv, 14–18.
28. STIEGLITZ, E. J.: Hypertension in pregnancy, relation of calcium content of blood to etiology, Arch. Int. Med., 1927, xxxix, 465–474.
29. HÜLSE, W., and STRAUSS, H.: Zur Frage der Blutdrucksteigerung. V. Über die Wirkung höherer Eiweissspaltprodukte auf den Blutdruck und ihr Vorkommen im Blute bei hypertonischen Nierenkrankheiten, Ztschr. f. d. ges. exper. Med., 1924, xxxix, 426–461.
30. JACKSON, H., JR., SHERWOOD, D. W., and MOORE, O. J.: Blood peptide nitrogen in arterial hypertension, Jr. Biol. Chem., 1927, lxxiv, 231–233.
31. OLIVER, G., and SCHÄFER, E. A.: On the physiological action of extract of the suprarenal capsules, Jr. Physiol., 1895, xviii, 230–276.
32. VAQUEZ, H.: Hypertension, Congr. franç. de méd., 1904, vii, 338.
33. AUBERTIN, C., and AMBARD, L.: Lésions des capsules surrénales dans les néphrites avec hypertension, Bull. et mém. Soc. méd. d. hôp. de Paris, 1904, xxi, 175–181.
34. PHILPOT, A.: An investigation into the histological condition of the suprarenal glands in conditions associated with a high blood pressure, Quart. Jr. Med., 1909–10, iii, 34–51.
35. WIESEL, J.: Renale Herzhypertrophie und chromaffines System, Verhandl. des Kongr. f. inn. Med., 1907, xxiv, 221–229.
36. PARKINSON, P. R.: The activity of the suprarenal glands in relation to blood-pressures, Trans. Path. Soc. London, 1907, lviii, 187.
37. HÜLSE, W.: Untersuchungen über gefässverengernde Stoffe im Blute bei Hypertonien, Zentralbl. f. inn. Med., 1922, xlii, 1–7.
38. ELLIOTT, T. R.: Pathological changes in the adrenal glands, Quart. Jr. Med., 1914–15, viii, 47–89.
39. INGIER, A., and SCHMORL, G.: Über den Adrenalingehalt der Nebennieren, Deutsch. Arch. f. klin. Med., 1911, civ, 125–167.
40. OPPENHEIMER, B. S., and FISHBERG, A. M.: Association of hypertension with suprarenal tumors, Arch. Int. Med., 1924, xxxiv, 631–644.
41. MAYO, C. H.: Paroxysmal hypertension with tumor of retroperitoneal nerve; report of case, Jr. Am. Med. Assoc., 1927, lxxxix, 1047–1050.
42. PINCOFFS, M. C.: Paroxysmal hypertension, associated with suprarenal tumor, Trans. Assoc. Am. Phys., 1929, xliv, 295–300.

43. ANSELMINO, K. J., and HOFFMANN, F.: Nachweis der antidiuretischen Komponente des Hypophysenhinterlappenhormons und einer blutdrucksteigernden Substanz im Blute bei Nephropathie und Eklampsie der Schwangeren, Klin. Wchnschr., 1931, x, 1438–1441.
44. ANSELMINO, K. J., HOFFMANN, F., and KENNEDY, W. P.: Relation of hyperfunction of posterior lobe of hypophysis to eclampsia and nephropathy of pregnancy, Edinburgh Med. Jr., 1932, xxxix, 376–388.
45. CUSHING, H.: Basophil adenomas of pituitary body and their clinical manifestations (pituitary basophilism), Bull. Johns Hopkins Hosp., 1932, l, 137–195.
46. CUSHING, H.: Further notes on pituitary basophilism, Jr. Am. Med. Assoc., 1932, xcix, 281–284.
47. CUSHING, H.: "Dyspituitarism": twenty years later, with special consideration of pituitary adenomas, Arch. Int. Med., 1933, li, 487–557.
48. CUSHING, H.: Posterior pituitary activity from anatomical standpoint, Am. Jr. Path., 1933, ix, 539–548.
49. HURWITZ, D., and BULLOCK, L. T.: Personal communication.
50. PAGE, I. H.: Personal communication.
51. BERBLINGER, W.: Die Menge der basophilen Epithelien in der Adenohypophyse des Menschen bei chronischer Glomerulonephritis, entzündlicher Schrumpfniere, bei den Nephrosklerosen und bei Urämie, Virchow's Arch. f. path. Anat., 1929, cclxxv, 230–249.
52. KRAUS, E. J., and TRAUBE, O.: Über die Bedeutung der basophilen Zellen der menschlichen Hypophyse, Virchow's Arch. f. path. Anat., 1928, cclxviii, 315–345.
53. HÖPPLI, R.: Über das Strukturbild der menschlichen Hypophyse bei Nierenerkrankungen, Frankf. Ztschr. f. Path., 1922, xxvi, 22–49.
54. PLUMMER, H. S.: Blood-pressure and thyrotoxicosis, Trans. Assoc. Am. Phys., 1915, xxx, 450–457.
55. BOAS, E. P., and SHAPIRO, S.: Diastolic hypertension with increased basal metabolic rate, Jr. Am. Med. Assoc., 1925, lxxxiv, 1558–1560.
56. BOHN, H.: Untersuchungen zum Mechanismus des blassen Hochdrucks. I. Gefässverengernde Stoffe im Blute beim blassen Hochdruck, Ztschr. f. klin. Med., 1931, cxix, 100–139.
57. BOHN, H., and HAHN, F.: Untersuchungen zum Mechanismus des blassen Hochdrucks; blutdrucksteigernde Stoffe im Harn, insbesondere beim blassen und roten Hochdruck, Ztschr. f. klin. Med., 1933, cxxiii, 558–584.
58. BOHN, H.: Zum Mechanismus des blassen Hochdrucks, vasoaktive und antidiuretische Stoffe im Blut, Liquor und Harn, Kreatin und Kreatinin im Blut und Harn, Verhandl. d. deutsch. Gesellsch. f. inn. Med., 1933, xlv, 182–186.
59. BOHN, H.: Über den chemischen, nicht nervösen Mechanismus des blassen Hochdrucks, Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch., 1933, vi, 218–224.
60. MARX, H., and HEFKE, K.: Untersuchungen zur Pathogenese der Hypertonie, Klin. Wchnschr., 1933, xii, 1318–1322.
61. CAPPS, R. B., FERRIS, E. B., JR., TAYLOR, F. H. L., and WEISS, S.: Rôle of pressor substances in etiology of arterial hypertension, Proc. Soc. Exper. Biol. and Med., 1934, xxxi, 1106–1108.
62. DE WESSELOW, O. L. V. S., and GRIFFITHS, W. J.: On question of pressor bodies in blood of hypertensive subjects, Brit. Jr. Exper. Path., 1934, lv, 45–52.
63. WEISS, S., and MINOT, G. R.: Nutrition in relation to arteriosclerosis, Arteriosclerosis, 1933, The Macmillan Co., New York, p. 233.
64. JOHN, M.: Über die Beeinflussung des systolischen und diastolischen Blutdrucks durch Tabackrauchen, Ztschr. f. exper. Path. u. Therap., 1913, xiii, 352–366.
65. PILCHER, J. D., and SOLLMANN, T.: Studies on the vasomotor center. I. The effects of the nitrite group, Jr. Pharmacol. and Exper. Therap., 1914–15, vi, 323–330.

66. Hoskins, R. G., and Ranson, S. W.: The vasomotor reaction to nicotin: locus of stimulation, Jr. Pharmacol. and Exper. Therap., 1915, vii, 375–383.
67. Riseman, J. E. F., and Weiss, S.: Age and sex incidence of arterial hypertension, Am. Heart Jr., 1929, v, 172–190.
68. Tscherkess, A.: Experimentelle Beiträge zur Pathologie des Gefässsystems bei Bleivergiftung. I. Mitteilung: Über die Einwirkung von Bleisalzen auf die Gefässe isolierter Organe, Arch. f. exper. Path. u. Pharmakol., 1925, cviii, 220–229.
69. Aub, J. C., Fairhall, L. T., Minot, A. S., and Reznikoff, P.: Lead poisoning, 1925, Williams and Wilkins Co., Baltimore.
70. Elschnig, A.: Sehstörungen durch Bleivergiftung, Wien. med. Wchnschr., 1898, xlviii, 1305.
71. Harris, L. I.: A clinical study of the frequency of lead, turpentine and benzin poisoning in four hundred painters, Arch. Int. Med., 1918, xxii, 129.
72. Feil, A., and Heim de Balsac, R.: Quelle est la valeur diagnostique comparée des signes cliniques dans le saturnisme au début, Paris méd., 1923, xlvii, 466.
73. Hering, H. E.: Die Karotissinusreflexe auf Herz und Gefässe, 1927, Th. Steinkopff, Dresden and Leipzig.
74. Heymans, C.: Le sinus carotidien et les autres zones vasosensibles réflexogènes, 1929, H. K. Lewis and Co., London.
75. Koch, E.: Die reflektorische Selbststeuerung des Kreislaufes, 1931, Th. Steinkopff, Dresden and Leipzig.
76. Koch, E., Mies, H., and Nordmann, M.: Arterieller Hochdruck durch Dauerausschaltung der Blutdruckzügler, Ztschr. f. Kreislaufforsch., 1927, xix, 585.
77. Weiss, S., and Baker, J. P.: Carotid sinus reflex in health and disease; its rôle in causation of fainting and convulsions, Medicine, 1933, xii, 297–354.
78. Sunder-Plassmann, P.: Untersuchungen über den Bulbus carotidis bei Mensch und Tier im Hinblick auf die "Sinusreflexe" nach H. E. Hering; ein Vergleich mit anderen Gefässstrecken; die Histopathologie des Bulbus carotidis; das Glomus caroticum, Ztschr. f. d. ges. Anat., 1930, xciii, 567–622.
79. von Hasselbach, H.: Bestehen Beziehungen zwischen Veränderungen am Sinus caroticus und der Hypertonie? Beitr. z. path. Anat. u. z. allg. Path., 1931, lxxxvi, 369.
80. Keele, C. A.: Pathological changes in the carotid sinus and their relation to hypertension, Quart. Jr. Med., 1933, ii, 213–220.
81. Weiss, S.: Unpublished observations.
82. Ellis, L. B., and Weiss, S.: Measurement of capillary pressure under natural conditions and after arteriolar dilatation; in normal subjects and in patients with arterial hypertension and with arteriosclerosis, Jr. Clin. Invest., 1929, viii, 47–67.
83. Weiss, S., and Ellis, L. B.: Quantitative aspects and dynamics of circulatory mechanism in arterial hypertension, Am. Heart Jr., 1930, v, 448–468.
84. Fishberg, A. M.: Hypertension and nephritis, 3d Ed., 1934, Lea and Febiger, Philadelphia.
85. Patek, A., and Weiss, S.: Tonus of autonomic nervous system in arterial hypertension, New Eng. Jr. Med., 1931, ccv, 330–334.
86. von Monakow, P.: Blutdrucksteigerung und Niere, Deutsch. Arch. f. klin. Med., 1920, cxxxiii, 129–152.
87. Bordley, J., III, and Baker, B. M., Jr.: Consideration of arteriosclerosis of cerebral vessels and pathogenesis of hypertension, Bull. Johns Hopkins Hosp., 1926, xxxviii, 320–321; xxxix, 229–264.
88. Cutler, O. I.: Relation of arteriosclerosis of cerebral vessels to hypertension; distribution of arteries supplying pons and medulla, Arch. Path., 1928, v, 365–379.
89. Raab, W.: Hirnblutuntersuchungen bei Hypertonie, Ztschr. f. klin. Med., 1931, cxv, 577–581.
90. Moschcowitz, E.: Hypertension: its significance, relation to arteriosclerosis and nephritis and etiology, Am. Jr. Med. Sci., 1919, clviii, 668–684.

91. Stieglitz, E. J.: Emotional hypertension, Am. Jr. Med. Sci., 1930, clxxix, 775–782.
92. Weiss, S.: Interpretations of syndromes associated with arterial hypertension, New Eng. Jr. Med., 1932, ccvii, 165–173.
93. Riseman, J. E. F., and Weiss, S.: Symptomatology of arterial hypertension, Am. Jr. Med. Sci., 1930, clxxx, 47–59.
94. Davis, D.: Nature of symptoms in essential hypertension, Am. Jr. Med. Sci., 1931, clxxxi, 850–857.
95. Ayman, D., and Pratt, J. H.: Nature of symptoms associated with essential hypertension, Arch. Int. Med., 1931, xlvii, 675–687.
96. Dennig, H., Fischer, K., and Beringer, K.: Psyche und vegetatives Nervensystem, Deutsch. Arch. f. klin. Med., 1930, clxvii, 26–43.
97. Lange, F., and Wehner, E.: Das Herz bei Hypertonie und bei Arteriosklerose, Deutsch. Arch. f. klin. Med., 1928, clx, 45–62.
98. Alvarez, W. C.: Blood pressures in fifteen thousand university freshmen, Arch. Int. Med., 1923, xxxii, 17–30.
99. Diehl, H. S., and Sutherland, K. H.: Systolic blood pressures in young men, including special study of those with hypertension, Arch. Int. Med., 1925, xxxvi, 151–173.
100. (*a*) Kauffmann, F.: Kreislauf und Nervensystem, Deutsch. med. Wchnschr., 1933, lix, 989, 1034, 1121.
(*b*) Fleisch, A.: Die Regulierung des Stromvolumens nach dem Blutbedarf. Handbuch der normalen und pathologischen Physiologie, 1931, xvi, pt. 2, p. 1235, J. Springer, Berlin.
101. Hochrein, M.: Über den Kreislaufmechanismus bei der Hypertension, Arch. f. exper. Path. u. Pharmakol., 1928, cxxxiii, 325–384.
102. Volhard, F., and Suter, F.: Nieren und ableitende Harnwege, 1931, Julius Springer, Berlin.
103. Wiggers, C. J.: Physical and physiological aspects of arteriosclerosis and hypertension, Ann. Int. Med., 1932, vi, 12–30.
104. Traube, L.: Über den Zusammenhang von Herz- und Nieren-Krankheiten, 1856, A. Hirschwald, Berlin.
105. Pässler, and Heineke: Versuche zur Pathologie des Morbus Brightii, Verhandl. d. deutsch. path. Gesellsch., 1905, ix, 99.
106. Janeway, T. C.: Note on the blood-pressure changes following reduction of the renal arterial circulation, Proc. Soc. Exper. Biol. and Med., 1908–09, vi, 109–111.
107. Janeway, T. C.: Nephritic hypertension: clinical and experimental studies, Am. Jr. Med. Sci., 1913, cxlv, 625–656.
108. Cash, J. R.: Blood-pressure following reduction of renal substance with a note on simultaneous changes in blood-chemistry and blood-volume, Bull. Johns Hopkins Hosp., 1924, xxxv, 168–180.
109. Wood, J. E., Jr., and Ethridge, C.: Hypertension with arteriolar and glomerular changes in albino rat following subtotal nephrectomy, Proc. Soc. Exper. Biol. and Med., 1933, xxx, 1039–1041.
110. Hartman, F. W., Bolliger, A., and Doub, H. P.: Experimental nephritis produced by irradiation, Am. Jr. Med. Sci., 1926, clxxii, 487–500.
111. Pedersen, A. H.: A method of producing experimental chronic hypertension in the rabbit, Arch. Path. and Lab. Med., 1927, iii, 912.
112. Bell, E. T., and Pedersen, A. H.: The causes of hypertension, Ann. Int. Med., 1930, iv, 227–237.
113. Menendez, E. B.: Stase veineuse du rein normal ou énervé et hypertension artérielle, Compt. rend. Soc. de biol., 1933, cxiii, 461.
114. Goldblatt, H., Lynch, J., Hanzal, R. F., and Summerville, W. W.: Studies on experimental hypertension; production of persistent elevation of systolic blood pressure by means of renal ischemia, Jr. Exper. Med., 1934, lix, 347–379.

115. FAHR, T., *In* HENKE, F., and LUBARSCH, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, 1925, vi, pt. 1, p. 438, Julius Springer, Berlin.
116. LEVINE, S. A., and FULTON, M. N.: Relation of hypertension to mitral stenosis, Am. Jr. Med. Sci., 1928, clxxvi, 465–474.
117. GALLAVARDIN: La tension artérielle en clinique, 2d Ed., 1920, Paris.
118. WALDBOTT, G. L.: Hypertension associated with allergy, Jr. Am. Med. Assoc., 1930, xciv, 1390–1392.
119. BIENSTOCK: Die Hypertonie—eine chronisch-allergische Tierproteintoxikose. (Schlussfolgerungen aus einer Selbstbeobachtung.), München. med. Wchnschr., 1932, lxxix, 101–104.
120. WEITZ, W.: Zur Ätiologie der genuinen oder vasculären Hypertension, Ztschr. f. klin. Med., 1923, xcvi, 151–181.
121. WEITZ, W.: Studien an eineiigen Zwillingen, Ztschr. f. klin. Med., 1924–25, ci, 115–154.
122. DE NÁDOR-NIKITITS, E.: Sur l'étiologie de l'hypertension artérielle essentielle et de la sclérose rénale, Arch. d. mal. du coeur, 1925, xviii, 582–599.
123. Quoted from WILLIAMS, G. D.: Hereditary aspects of arterial hypertension in relation to arteriosclerosis, Arteriosclerosis, 1933, The Macmillan Co., New York, p. 537.
124. O'HARE, J. P., WALKER, W. G., and VICKERS, M. C.: Heredity and hypertension, Jr. Am. Med. Assoc., 1924, lxxxiii, 27–28.
125. AYMAN, D.: Heredity in arteriolar (essential) hypertension: a clinical study of the blood pressure of 1,524 members of 277 families, Arch. Int. Med., 1934, liii, 792–802.
126. WEISS, S.: The interaction between emotional states and the cardiovascular system in health and in disease, 1932, iii, 1181, Emanuel Libman Anniversary Volumes, International Press, New York.

INFLUENTIAL FACTORS IN RECOVERY FROM RHEUMATOID ARTHRITIS*

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EVERY physician knows that there is more than one factor which enters into recovery from an infectious disease. These various factors are constitutional or environmental. It occurred to me that it might be interesting to consider at this time the more important factors which influence recovery in one of our commoner infections, namely rheumatoid arthritis. At the outset some may object to the assumption that rheumatoid arthritis is a chronic infection. It must be admitted that the evidence for its infectious nature is not complete, but the fact remains that the majority of investigators in this field now consider it a chronic infection, and the writer will therefore discuss the disease from the infectious point of view in the present paper.

Any kind of discussion of rheumatoid arthritis is always handicapped by the fact that we know so little concerning the origin and nature of the disease. In observing a patient with rheumatoid arthritis we see pathologic changes and symptoms which bear all the earmarks of a chronic infection. But just *why* the patient develops the disease, or exactly *how* he develops it are still subjects for speculation. This, of course, is true of other infections which are better understood than rheumatoid arthritis. "First causes" in medicine are always problematical. Let us, therefore, concern ourselves no longer with the teleology of this disease, but proceed at once to a discussion of the factors which influence, or appear to influence, recovery from it.

CONSTITUTION

We can do no better than begin with constitution. Is there such a thing as a constitutional diathesis toward rheumatoid arthritis? The writer believes that there is. I have seen too many long lanky men and women with the disease to question the tendency of this type toward rheumatoid infection. This of course is the so-called tuberculous type and raises the question whether there is any basis for the contention now being made by certain German writers that rheumatoid arthritis is a form of tuberculosis. One sees stocky, and even obese, patients in an arthritis clinic, but most of them are suffering from hypertrophic rather than from rheumatoid arthritis, and many of the rheumatoid patients who appear rotund have been slender and long-trunked in their younger days. I would not deny, of course, that the stocky, so-called brachycephalic type can develop rheumatoid arthritis, but I think it is an exception to the rule, and I am quite sure that the stocky type responds more readily to treatment than do the dolichocephalics.

*Read at the Chicago meeting of the American College of Physicians, April 19, 1934.

Temperament

Closely allied to constitution is the question of temperament. Neurotic, introspective patients are more difficult to relieve than buoyant cheerful ones. The natural melancholy of the Jewish race has always seemed to me a distinct handicap to their recovery from rheumatoid arthritis, though here again there are many exceptions. I have often wondered why so many spinsters develop the rheumatoid syndrome. I doubt if the sex hormones are influential in this connection. It appears more likely that the really predisposing factor is the temperament of the patient.

Heredity

There is great need for a thorough-going, scientific study of heredity in relation to rheumatoid arthritis. There are very few articles on this subject in medical literature. Marinesco and Allende [1] have recently reported the cases of two brothers and a sister, all of whom developed in the early years of their childhood the deforming type of chronic infectious arthritis, so-called Still's disease. The writer recalls from his own experience two families in which the incidence of rheumatoid arthritis was amazingly high. In one of these families the disease could be accurately traced through four generations. (Table 1.) Such extreme examples are unusual, but the hereditary factor may be more important than we have realized. Certainly a great many of the writer's patients testify that one or both of their parents suffered from chronic arthritis. The difficulty arises in determining what type of arthritis the parent had: that is, whether it was rheumatoid or hypertrophic in character. Some of our young students of arthritis could hardly find a more interesting problem for investigation than the rôle of heredity in rheumatoid arthritis. I should add that in those cases where heredity appears to play an important part, the patient often progresses to the deforming and ankylosing stage of the disease in spite of all treatment.

Race

So far as the writer knows, no *race* is immune to rheumatoid arthritis. I suspect that the dark races are less susceptible than the white races, but this may be due to differences of habits or environment rather than to any variations in racial immunity.

Age

Rheumatoid arthritis may develop at any age and may be a formidable menace to health at any age. Cecil and Archer [2] found the highest incidence of onset was at 35. So far as recovery is concerned, I used to think that young adults offered a better prognosis than patients who developed the syndrome late in life. With increasing experience, however, I am not so

TABLE I

Incidence of Rheumatoid Arthritis in One Family

G. G. M. Spondylitis deformans (all her life).

G. M. Poker back and arthritis in knees from 20 on.

10 children Lived to maturity.

Five had no arthritis in youth, but all developed senescent arthritis. (F) Partially bedridden at 27.

T. F. (M) Rheumatoid arthritis. Bedridden at 28. (F) All right at 29.

C. F. (M) Rheumatoid arthritis. Developed at 35. (M) All right at 21. (F) All right at 17.

S. F. J. (F) 2 attacks acute rheumatoid arthritis. At 54 no joint symptoms. No children.

E. F. C. (F) Onset rheumatoid arthritis at 33. Bedridden at 56 with marked deformities. No children.

R. F. M. (F) At 42 developed pain and stiffness in neck and deforming arthritis of fingers. (F) All right at 28. (F) Onset rheumatoid arthritis at 24. Chronic sinusitis.

thoroughly convinced on this point. I have recently seen several patients who developed rheumatoid arthritis after 60, and who have responded promptly to treatment. Tuberculosis is supposed to deal more kindly with the middle-aged and elderly than with young adults, and the same may be true of rheumatoid arthritis. This point can be settled only by careful statistical studies. Middle-aged and elderly patients are more coöperative than young people and follow the physician's instructions more carefully. On the other hand, they often have to contend with a coexisting osteoarthritis, which may set up a sort of vicious circle in the joints affected.

Sex

I am sorry to say that I have no figures on the incidence of recovery from rheumatoid arthritis with respect to sex. We do know that women are two or three times as susceptible to the disease as are men, and my impression is that in general men respond more quickly to treatment than do women.

Climate

The final chapter on the relation of climate to the incidence of rheumatoid arthritis and to recovery from this disease has yet to be written. It is claimed, and I suspect rightly, that the natives of Arizona and New Mexico never develop rheumatoid arthritis. It is rarely seen in the tropics, though I believe it is fairly common in some of our southern cities, such as New Orleans. Certainly it is commoner in the southern part of the United States than rheumatic fever. We have yet to determine, however, just how much better the prognosis of the rheumatoid patient is in Arizona than it is in the eastern part of the United States, assuming that the other environmental factors are the same. What I mean to say is this: How much higher is the percentage of recovery for arthritic patients in an Arizona sanatorium than it would be for patients in a New York or Pennsylvania sanatorium? This question can be answered only by carefully prepared statistical and follow-up studies. Theoretically Arizona, because of its wonderful climate, should have the best of it, but unfortunately even Arizona fails with many of our more stubborn cases.

Economic Status

Rheumatoid arthritis is like tuberculosis and rheumatic fever. It is more prevalent among the poor than among the well-to-do, and the former do not respond so well to treatment. The poor are more exposed to cold and damp weather; their food is not so well cooked, their diet often poorly balanced. They have not the means of getting proper medical attention, and more important still, they have not the time or money for rest cures.

Joints Involved

The outcome in rheumatoid arthritis depends to some extent on the joints involved. When the fingers are first attacked it often seems to confer some immunity against involvement of the larger joints. The knees are bad joints mechanically and always present a difficult problem, not only because of the intricacy and size of the joint, but because it is a weight-bearing joint. I have often noticed that in convalescent patients the knees and feet will be the last to recover, usually because the patient becomes restless, discontinues rest and starts walking before the joints have healed completely. The hip is usually one of the last joints to be affected in rheumatoid arthritis, and this is indeed fortunate, because infection of the hip joint is painful and yields very slowly to treatment.

Perhaps the most stubborn of all is the infectious spondylitis of the Marie-Strümpell type. "Poker spine" is a hard disease to check. It occurs almost exclusively in young males and often runs a rapidly progressive course, producing marked rigidity of the spine and ankylosis of the shoulders and hips.

Effect of Other Diseases on Development and Course of Rheumatoid Arthritis

I have recently become interested in investigating the effect of other diseases on the incidence and course of rheumatoid arthritis.

Focal Infection. I suppose no one would deny the importance of focal infection in the etiology and course of rheumatoid arthritis. The fact that the removal of foci of infection does not always lead to recovery from arthritis detracts in no way from its significance. A great many people carry foci of infection for years without any joint symptoms. A certain number will develop arthritis. Why some get the disease and others escape, we do not know, but we cannot avoid the conclusion that focal infection is an important predisposing factor in the etiology of rheumatoid arthritis and that the elimination of such foci is a fundamental step on the road to recovery.

Pulmonary Tuberculosis. Rheumatoid arthritis is comparatively rare in tuberculous patients. Pemberton[3] is my authority for this statement, which is in agreement with my own personal experience. The two diseases do occur, however, in the same patient as the following example will show:

Case Report (Abstract)

Rheumatoid Arthritis and Pulmonary Tuberculosis

R.H. Female. Aged 26.

July 1930—Migratory progressive pain and swelling of joints.
Nov. 1930—Hemorrhage. Diagnosis: Pulmonary tuberculosis.

Summer, 1931—Saranac. "Extensive pulmonary tuberculosis." Pain and swelling of joints.
1932 to 1933—At Saranac. Marked improvement in both conditions. Became practically free of symptoms.
May 1933—Return of pain and swelling of joints.
Râles at left apex.
Agglutination *Streptococcus hemolyticus* 1:320. Sedimentation rate 1.3. W.B.C. 8,000. Tonsils out. Vaccine, etc.
March 1934—No signs of tuberculosis. Practically free of joint symptoms.

The arthritis in this case never presented the picture of a tuberculous infection. Furthermore the agglutinins for *Streptococcus hemolyticus* in the patient's serum identified the disease as rheumatoid arthritis.

Syphilis. When chronic arthritis develops in a syphilitic patient, one must be sure that he is not dealing with a syphilitic arthritis. This differentiation, however, is usually easy as luetic arthritis, like tuberculous arthritis, usually involves only one joint. The following case presented all the symptoms and signs of rheumatoid arthritis and occurred in a patient with a strongly positive Wassermann.

CASE REPORT (ABSTRACT)

Rheumatoid Arthritis and Syphilis

G. D. Female. Aged 44.

1925—Onset of rheumatoid arthritis.
April 1930—First seen by writer. Mild rheumatoid arthritis. Chronic sinusitis. Several fusiform fingers. Agglutination: *Streptococcus hemolyticus* 1:1280.
April 1931—No improvement after one year of routine treatment.
Wassermann 4 plus (controlled).
Husband 4 plus.
Salvarsan and bismuth.
Oct. 1931—Rapid disappearance of all arthritic symptoms.

The improvement in the arthritis was so marked after the introduction of specific therapy that one might have suspected this of being a luetic arthritis but for the high agglutination with *Streptococcus hemolyticus.* The chronic focus in the sinus and the typical fusiform fingers also supported the diagnosis of rheumatoid arthritis. It seems fair to assume that in this case rheumatoid arthritis developed in a patient whose resistance had been lowered by a previous luetic infection and that when the latter was brought under control by specific therapy, the patient soon got control also of the arthritic condition. We might also suspect that in this case the arsenic in the salvarsan was of distinct benefit to the arthritic as well as to the syphilitic infection.

Rheumatic Fever. It would not be appropriate in this discussion to take up the relationship of rheumatic fever to rheumatoid arthritis. This question has recently been discussed at length by Dawson,[4] who believes that the two diseases are very similar in character. We do know that a few

cases of rheumatic fever progress into a condition indistinguishable from rheumatoid arthritis. I can recall one young man in my own practice who, subsequent to rheumatic fever, developed rheumatoid arthritis and, after suffering with it for two or three years, finally made a complete recovery. His only residual lesion was a severe mitral endocarditis.

Gout. The etiology of gout is still a subject of much debate. Some writers speak of it as a metabolic disease. Others consider it an allergic condition, and still others an infection. The writer is quite sure that on more than one occasion he has encountered rheumatoid arthritis and gout in the same patient. The following two cases will serve as good examples:

CASE REPORT (ABSTRACT)

Rheumatoid Arthritis and Gout

J. W. Male. Aged 39.

1913—Acute gout in great toe.
1913 to 1928—Sporadic attacks in right great toe. Becoming more frequent.
1928 to 1932—Attacks of polyarthritis.
June 23, 1932—First seen by writer. Chronic podagra. Arthritis of ankles and knuckles. Fusiform joint, left ring finger. Uric acid 6.5 mg. Agglutination *Streptococcus hemolyticus* 1:2560. *Streptococcus hemolyticus* 3 plus positive in throat culture.
July 26, 1933—Much improved after a year of treatment. Agglutination *Streptococcus hemolyticus* neg. Uric acid 4.3 mg.
1933 to 1934—Occasional attacks of gout, but arthritis no longer active.

This patient undoubtedly had gout, and the high agglutination with the *Streptococcus hemolyticus* pointed strongly toward a concomitant rheumatoid arthritis. The swelling and pain in various joints and the fusiform ring finger were also strongly indicative of rheumatoid arthritis.

CASE REPORT (ABSTRACT)

Rheumatoid Arthritis and Gout

R. S. R. Male. Aged 51.

July 1931—Progressive polyarthritis with swelling, fusiform fingers, etc.
Jan. 1932—First seen by writer. Typical rheumatoid arthritis. Agglutination *Streptococcus hemolyticus* neg. Sedimentation rate 1.2 mm. Uric acid 4.2 mg.
April 1933—Arthritis much improved. Fusiform fingers almost disappeared. Sedimentation rate 1.5 mm.
Sept. 1933—Arthritis much improved, but patient has developed typical gouty bursitis on both elbows. Colchicum, atophan, etc. Uric acid 5.1 mg.
Jan. 1934—Feeling fine; gaining weight. "Bags" on elbows much smaller. Sedimentation rate 0.8 mm. Uric acid 3.7 mg.
April 1934—Relapse. Pain and swelling in toes, elbows and right hip. Sedimentation rate 1.6 mm. Uric acid 5.0 mg.

This patient is still under observation. He is slowly recovering from

a severe joint condition, one which I and others thought would surely result in permanent crippling.

Pernicious Anemia. The writer has no very definite impressions concerning the effect of a coincident pernicious anemia on the course of rheumatoid arthritis. An appeal to my friend, Dr. George Minot,[5] brought the following interesting reply, which I have his permission to quote:

> The patient was a woman of about 60 years of age with typical pernicious anemia, whom I had suspected of having pernicious anemia several years before treatment was begun. Typical rheumatoid arthritis had existed for at least five years in a mild form. Under treatment with liver extract, the blood picture returned to normal. About the time the blood became normal, there was a sharp exacerbation in the rheumatoid arthritis. During the period of improvement her appetite was vastly better than it had been for many years, and she gained a moderate amount of weight. For the flare-up in her arthritis a rest program and a diet containing fewer calories were prescribed. After approximately six months the rheumatoid arthritis had lost its intensity and she was definitely better. At a later date this patient gave up liver, of her own accord, and relapsed. The arthritis remained quiescent, but increased in intensity as she got better again. This all happened over four years ago. I saw her about four months ago and she has remained in good health.
>
> On the contrary, there are other cases I can cite where practically the reverse state of affairs took place. One was a female 40 years old. Arthritis in this instance was the presenting symptomatology of long duration, certainly five years. The anemia developed slowly; at first it was thought to be hypochromic; examination, however, showed it to be macrocytic. Tongue symptoms appeared. Increased rheumatoid arthritis was obvious at the time the blood was low (approximately two million red cells per cu. mm.) and in this instance, coincident with return of the blood to normal, the arthritis improved pronouncedly. In this latter case the individual was definitely under-weight; in the former case the patient was a little over-weight, even during the relapse in pernicious anemia.

Dr. Minot feels as I do, that without many more case studies, we can say nothing definite about the relation between these two diseases.

Psoriasis. The frequent coexistence of psoriasis and rheumatoid arthritis has long been a subject for comment. The writer has the impression (which, however, is not based on statistics) that few if any of the arthritics with psoriasis ever make a complete and permanent cure of either disease, though they may improve under treatment. In the German and French literature this syndrome is spoken of as *arthritis psoriatica.* Bauer and Vogl[6] showed that in certain families, some members were suffering from psoriasis only; some from a polyarthritis only; while some presented the combined syndrome. They further claim that different types of joint diseases are to be met with in patients suffering from psoriasis, though they admit that the arthritis is usually of the chronic infectious or rheumatoid type. In one family Bauer and Vogl encountered an intermittent hydrops in association with psoriasis. Several other members of the family also had psoriasis and one of these suffered in addition from rheumatoid arthritis.

The following two synopses are taken from my own case records:

CASE REPORT (ABSTRACT)

Rheumatoid Arthritis and Psoriasis

J. M. Female. Aged 25. Psoriasis since age of 7.

1918—Gradual onset of rheumatoid arthritis.
Oct. 1927—Severe rheumatoid arthritis. Psoriasis all over body.
Nov. 1927—Tonsillectomy, streptococcus vaccine, etc.
Jan. 1928—Joints improving. Psoriasis better.
Sept. 1928—Recurrence of arthritis. Return of psoriasis.
Jan. 1929—Feeling fine. Slight improvement in psoriasis.
April 1929—Some pain in joints. Increase in psoriasis.
Dec. 1929—Return of symptoms in joints and more psoriasis.
Dec. 1930—Pain in back and joints. Psoriasis troublesome.
Jan. 1931—Joints comfortable. Much less psoriasis.
March 1934—Arthritis much improved. Psoriasis persists.

CASE REPORT (ABSTRACT)

Rheumatoid Arthritis and Psoriasis

A. T. Male. Aged 47.

1915—Gradual development of rheumatoid arthritis. Psoriasis appeared about same time.
1924 to 1926—Almost free of symptoms. "Psoriasis always better when joints are better."
1927—Return of arthritis.
Jan. 1931—First seen by writer. Extensive rheumatoid arthritis. Spots of psoriasis all over body. Streptococcus vaccine intravenously, diet, etc.
March 1931—Much improved. Psoriasis fading. Scales disappearing.
April 1931—Steady improvement in joints and in psoriasis.
Sept. 1931—Practically free of symptoms. Psoriasis almost gone.

These two case histories illustrate a fact that I have long recognized, namely that arthritis and psoriasis improve or regress together. I have seen a good many patients with rheumatoid arthritis and psoriasis, and I feel moderately certain that when one condition improves, the other improves.

Hyperthyroidism. A good deal has been written about the relation of arthritis to the thyroid gland, but there is no convincing proof of any connection between the two. The following case, however, has certain points of interest:

CASE REPORT (ABSTRACT)

Rheumatoid Arthritis and Hyperthyroidism

W. J. Male. Aged 29.

May 1929—Onset of rheumatoid arthritis.
Jan. 1930—Sinus operation. Rest in hospital 2 months. Florida 2 months.
June 1930—Returned to work.
Aug. 1930—Relapse.
Oct. 1930—First seen by writer. Severe rheumatoid arthritis and spondylitis. Agglutination *Streptococcus hemolyticus* 1:160.

Nov. 1930—Tucson.
Dec. 1930—B.M. plus 35 (controlled). Weight 92 lbs.
Feb. 1931—Thyroidectomy.
Dec. 1931—Remarkable and complete recovery except for some residual stiffness in spine.

The improvement in this patient's condition following thyroidectomy was quite remarkable. One would expect a priori that a high basal metabolism would react favorably in a patient with rheumatoid arthritis. Indeed, thyroid extract has been recommended by more than one authority as a valuable agent in the treatment of rheumatoid arthritis. In this particular case, however, the arthritis progressed unfavorably in spite of all treatment until the metabolism was brought back to normal by thyroidectomy.

Diabetes. Diabetes is a much commoner associate of hypertrophic arthritis than it is of the rheumatoid type. The coexistence of diabetes with rheumatoid arthritis is of particular interest in view of Pemberton's[7] claims that the sugar tolerance is low in this form of joint disease. The following case illustrates the coincidence of diabetes and rheumatoid arthritis:

CASE REPORT (ABSTRACT)

Rheumatoid Arthritis and Diabetes

W. L. Male. Aged 54.

1925—Chronic sore throat. Onset of diabetes. 20 units of insulin daily.
1926—Gradual development of pain in knees and feet.
Jan. 1930—Rapid onset of rheumatoid arthritis affecting many joints.
May 9, 1930—First seen by writer. Many joints swollen. Blood sugar 238 mg. Urine showed trace of sugar.
June 6, 1930—Treatment for arthritis started; vaccine, diet, etc.
June 13, 1930—Tonsils removed.
July 15, 1930—Joint condition improving steadily. Blood sugar 200 mg. Urine free from sugar.
Aug. 6, 1930—Joints continue to improve. Goes on a vacation.
November 1930—Patient died suddenly; cause unknown.

TREATMENT

No discussion of the factors influencing recovery from rheumatoid arthritis would be complete without some consideration of the method of treating the disease. The method of treatment varies a great deal in different localities, and it would be beyond the scope of this article to discuss in detail these various methods of treating rheumatoid arthritis. There are certain fundamental phases of the treatment, however, that have an important influence on the course of the disease.

For example, with regard to foci of infection. A good deal depends upon *when* and *how* the focus in question is removed. For example, a focus removed early in the disease often leads to a permanent recovery from

the arthritis, while one removed two or more years after the onset of the joint symptoms rarely produces a favorable effect on the disease. Then so much depends on *how* foci are removed. The writer could cite more than one instance of sharp exacerbation of joint symptoms following tonsillectomy by an inexperienced or unskillful operator. I know of no operation where gentle handling of the infected tissue is more important. On the other hand I could cite one or two laryngologists who so far as I know have never produced a flare-up in an arthritic patient after the removal of tonsils. This has convinced me that good results following tonsillectomy depend a great deal on who removes the tonsils. Perhaps what has been said about tonsils applies even more in the case of surgery of the sinuses. Operations on the ethmoid and sphenoid cells are difficult at best and certainly require the utmost skill on the part of the operator if good drainage is to be established. In patients who have multiple root abscesses, it is better not to extract all the infected teeth at one sitting. Exacerbations in the joints have been known to follow such radical treatment.

If space permitted, a great deal could be said about the importance of coöperation on the part of the patient, and also concerning the choice of a physician. I would like to say one thing about the latter. I am not very sympathetic with the so-called arthritis specialist, that is, with the practitioner who devotes himself exclusively to treating this one disease. He will probably give his patients better treatment if he is a good all-round internist. I do say, however, that the patient with arthritis is wise if he seeks the counsel of a physician who is interested in this disease. The treatment of chronic arthritis, like that of the other great systemic diseases, presents a complex medical problem, and with it go the various specialized forms of therapy, such as control of diet, physiotherapy, intravenous vaccines, orthopedic measures, etc. Personally I believe that the time is not far off when every state in the Union will have specially equipped sanatoriums for the treatment of arthritis, similar to those which now exist for the treatment of tuberculosis. When that day comes, it is reasonable to believe that the chronic arthritic will fare much better than he does at present.

Summary

In this brief discussion, I have tried to sum up the various factors which predispose to, and influence the course of, rheumatoid arthritis. We have seen that these factors may be either constitutional, such as race, temperament, heredity, sex, age or some constitutional disease; or they may be entirely environmental, depending on the economic status of the patient, his place of abode, the type of doctor he selects, and the kind of treatment he receives.

When we consider the multiplicity of factors which enter into recovery from this baffling disease, the need of concentrated and specialized care for rheumatoid patients becomes all the more obvious. In the opinion of the

writer, a considerable proportion of them should be treated in sanatoria especially equipped for the care of rheumatoid cases.

REFERENCES

1. Marinesco, G., and Allende, G.: Sur une forme nouvelle de rhumatisme chronique fibreux, rhumatisme chronique, familial et infantile, Presse méd., 1932, xl, 646–649.
2. Cecil, R. L., and Archer, B. H.: Chronic infectious arthritis; analysis of 200 cases, Am. Jr. Med. Sci., 1927, clxxiii, 258–270.
3. Pemberton, R.: Arthritis and rheumatoid conditions, 1929, Lea and Febiger, Philadelphia.
4. Dawson, M. H.: Comparative study of subcutaneous nodules in rheumatic fever and rheumatoid arthritis, Jr. Exper. Med., 1933, lvii, 845–858.
5. Minot, G.: By personal communication.
6. Bauer, J., and Vogl, A.: Psoriasis und Gelenkleiden, Klin. Wchnschr., 1931, x, 1700–1705.
7. Pemberton, R., and Foster, G. L.: Studies on arthritis in Army, based on 400 cases, Arch. Int. Med., 1920, xxv, 243.

CARDIOVASCULAR OBSERVATIONS IN 215 NEUROSYPHILITICS*

By Clough Turrill Burnett, M.D., F.A.C.P., and Charles A. Rymer, M.D., *Denver, Colorado*

The subject of this paper, cardiovascular syphilis, offers an interesting example of a tendency to search for the new while at times forgetting the old teachings. Aortic aneurysm appears after the introduction of syphilis into Europe subsequent to the return of Columbus and the occupation of Naples by the army of Charles VIII in 1495. Some sort of association with syphilis was mentioned by Fernelius in 1542, by Vesalius in 1557, and by Paré in 1582, who associated aneurysm with the "French disease." Morgagni (1682–1771) noted the association of aortic disease with syphilis. He first described a case of heart-block and what was later known as the Stokes-Adams syndrome. Then the luetic origin of aortic aneurysm was forgotten until nearly the middle of the past century, although Osler states that syphilis of the heart was mentioned as far back as 1736. French writers claim that Ricord, who was American born, first described definite cardiac gumma in 1845. However, accurate knowledge of cardiovascular syphilis is but little more than 50 years old, and 20 years ago there was practically no mention of the subject in current textbooks. There appears to have been a definite increase since the war and, either because of this or improved methods of diagnosis, it has occupied an important place in recent medical literature.†

Frequency of Cardiovascular Syphilis

Numerous authors have discussed this subject with a wide divergence of opinion. The relation of cardiovascular syphilis to all forms of heart disease is given by Coombs [1] as 5 to 15 per cent and by Moore, Danglade and Reisinger [2] as 10 to 15 per cent. In general autopsy statistics cardiovascular syphilis appears according to different observers in 2 to 6 per cent of the cases examined. Aortic syphilis was observed at autopsy in late syphilis in 20.5 per cent of the cases examined by Coombs.[1] Moore and his associates [3] quote Langer, of Germany, to the effect that 70 to 80 per cent of all syphilitics show aortitis, aortic insufficiency or aneurysm, and that 50 per cent of all aortic insufficiency is syphilitic. Moore also advances the opinion that 80 to 90 per cent of all late syphilitics show evidence of aortic syphilis. Warthin [4, 5, 6] teaches that aortitis with aneurysm or aortic insufficiency occurs in some degree in the aorta of every male syphilitic and,

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† Since this was written, a most comprehensive review of the literature on cardiovascular syphilis has been presented by Dr. Lewis A. Conner in the Jr. Am. Med. Assoc., 1934, cii, 575, to which those interested are referred.

considering this frequency, that aneurysm and aortic insufficiency are rare occurrences in the history of aortic syphilis, and that these when present are due to functional stress. A more startling statement of the same author is as to the occurrence of syphilitic involvement of the heart. Briefly, this is that the spirochete is constantly present in the heart muscle of all cases of latent syphilis. In the congenital syphilitic heart the spirochete is demonstrated with some facility; but in the acquired form, while he states that the spirochete is constantly present, the demonstration of these organisms may require the utmost patience and considerable time—often weeks. Friedman [7] quotes numerous authors as showing that vascular changes are noted in from 49 to 76 per cent of cases of visceral syphilis. The per cent in which thoracic aneurysm is syphilitic is given by Coombs [1] and Lendon [8] as 75, and of abdominal aneurysm 35 by the former and 33.3 by the latter author. Moore and his coworkers [3] state that 10 per cent of tertiary syphilitics show cardiovascular syphilis clinically but only 3.8 per cent of the cases of uncomplicated aortitis were correctly diagnosed antemortem, while according to Jagic [9] only 2 per cent were clinically diagnosable. Grassman, quoted by Turner and White,[10] found that in 288 cases of secondary syphilis arrhythmias or pulse disturbances were noted in 85 per cent and murmurs in 40 per cent. Amelung and Sternberg [10] believe the above figures too high. They studied 275 early cases for one year and noted heart enlargement (confirmed by roentgen-ray) sound changes, tachycardia, premature contractions or murmurs, in 21 per cent. In this group was one case of aortic insufficiency, which was recognized clinically, and two proved at autopsy. Brooks [11] reports 2 cases of aortic aneurysm within six months of the primary lesion, and has in another report [12] recorded 24 of 300 cases of cardiac lues occurring in the secondary stage. Moore [13] noted precordial pain of a few days' duration in a secondary case which subsided under specific therapy. But opinions differ widely. Turner and White [10] report a study of 50 cases of primary and secondary syphilis, excluding all cases over 40 years to eliminate coronary sclerosis. There were no cases of hypertension or recognized arteriosclerosis and, so far as possible, other infections were excluded. They found no definite clinical evidence of cardiovascular disease and conclude that "a critical study of the literature shows that clinical evidence of cardiovascular disease in early syphilis is rare."

Wile and Marshall,[14] Friedman,[7] Lucke and Rea,[15] et al., have called attention to an apparent selective affinity of the spirochete for certain tissues and to the fact that, dependent upon individual and racial differences, certain tissues appear to bear the brunt of the attack. Musser and Bennett [16] describe a vasotrophic and neurotrophic strain of spirochetes.

Concomitance of Cardiovascular Syphilis and Neurosyphilis

It is with this subject that the present study is especially concerned. Here again opinions differ widely as to the frequency of this association.

The frequency of occurrence of neurosyphilis in cardiovascular syphilis is given as follows: Lendon [8]—10 per cent in whites; Riven and Feigenbaum [17]—10 per cent; White [18]—16 to 20 per cent with 33.3 per cent on pathological evidence; Coombs [19] quotes Hubert as reporting 25 per cent of 300 cases of cardiac syphilis as also having tabes. Moore [2] states that while not all patients with cardiovascular syphilis have tabes, practically all tabetic patients have syphilitic aortitis. On this point—namely, the occurrence of cardiovascular syphilis in neurosyphilis—there is similar divergence of opinion from Friedman's [7] statement of 10 to 20 per cent to Kurtz and Eyster's [20] report of the finding by fluoroscopic means of aortitis in 95.7 per cent and of aneurysms in 21.8 per cent of their cases of neurosyphilis. In view of this wide difference, we concluded that an especial study of this relationship might explain this discrepancy and furnish an acceptable percentage of concomitance.

Purpose of the Present Study

1. To determine the frequency of cardiovascular syphilis in neurosyphilis.
2. To determine the frequency of diagnosable cardiovascular syphilis in neurosyphilis.
3. To determine the value of the electrocardiogram in the diagnosis of cardiovascular syphilis.

Material

The data in this report are based upon a study of 215 cases of neurosyphilis in the Colorado Psychopathic Hospital at Denver between October 1929, and September 1933. These cases are divided into paresis, tabo-paresis, tabes dorsalis, and meningo-vascular syphilis as follows:

A. Paretics	145	67.4 per cent
B. Tabo-paretics	15	6.8
C. Tabes	18	8.3
D. Meningo-vascular syphilis	37	17.5
Total	215	

Each case was further grouped as follows:

Group I	Physical and roentgen-ray findings normal.
Group II	Physical findings abnormal, roentgen-ray normal.
Group III	Physical findings normal, roentgen-ray abnormal.
Group IV	Physical findings abnormal, roentgen-ray abnormal.

Each case had a careful historical investigation, was examined by one or two physicians, and in all questionable cases by a consulting internist. All patients showing any historical or clinical evidence of rheumatic heart disease (10 cases) were excluded, as were also five cases insufficiently

studied for inclusion in this series. As a control group we studied in a similar complete manner 100 consecutive non-syphilitic cases in the same hospital.

TABLE I

To show the age distribution of the entire group of 215 cases with reference to Groups A (Paretic), B (Tabo-Paretic), C (Tabetic), D (Meningo-Vascular); and Classes I (Normal Physical), (Normal X-Ray) II (Abnormal Physical), (Normal X-Ray) III (Normal Physical), (Abnormal X-Ray) IV (Abnormal Physical). (Abnormal X-Ray)

Groups	Totals	Ages 21–30				Ages 31–40				Ages 41–50				Ages 51–60				Ages 61–70			
		I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III	IV
A. PARETIC																					
Number of cases.....	145	9				45	1	1	3	28	2	10	7	10	3	6	8	5	2	3	2
Percentage of 215 cases	67.4	4.1				20.9	0.5	0.5	1.5	13.0	0.9	4.6	3.2	4.6	1.3	2.6	3.7	2.3	0.9	1.3	0.9
B. TABO-PARETIC																					
Number of cases.....	15	1								3	1			4	1	1	2	1			1
Percentage of 215 cases	6.8	0.4								1.3	0.4			1.8	0.5	0.5	0.9	0.5			0.5
C. TABETIC																					
Number of cases.....	18					2				7		2		4	1	1	1				
Percentage of 215 cases	8.3					0.9				3.2		0.9		3.2	0.5	0.5	0.5				
D. MENINGO-VASCULAR																					
Number of cases.....	37	4				11			1	4	2	5	1	3		2	3	1			
Percentage of 215 cases	17.5	1.8				5.0			0.5	1.8	0.9	2.3	0.5	1.3		0.9	1.3	0.5			

Table 1 shows:

1. That a very large proportion (62.8 per cent) of these cases occur in the fourth and fifth decades and 6.3 per cent in the third decade before arteriosclerotic changes are of significance. The average age was 45 years.

2. That 33.9 per cent of the entire series occur among paretics between 31 and 50 (20.9 per cent 31–40) and that the cases included in this percentage are not diagnosed by physical or roentgen-ray methods.

3. That 31.4 per cent of the syphilitic group occur after 50; 64 per cent of our controls fall in the fourth and fifth decades (31–50), 16 per cent before 30, and 20 per cent after 50.

Of the 215 cases of neurosyphilis 73, or 33.9 per cent, showed some form of cardiovascular pathology independent of the electrocardiogram. Of these 73 cases 57 were complicated and uncomplicated aortitis. Of the remaining 16 cases three showed myocarditis without aortitis, five hypertensive heart disease, and eight were unclassified.

Table 6, in which appears a summary of all autopsy reports on this complete series, presents a check on the accuracy of the clinical diagnoses. Of the 14 cases coming to autopsy, in two only were the clinical findings not verified at autopsy; in these we failed to recognize an aortitis when present. While this is a small number of autopsies it represents reports on 42 per cent of those who have died, and furnishes a fairly good check on the accuracy of the diagnosis of aortitis in this institution.

TABLE II

Relationship of Aortitis and Aortitis with Complications to Electrocardiographic Changes

Groups	Aortitis	Aortic Insufficiency with Aortitis	Aortitis with Hypertensive Heart Disease	Aortitis with Myocarditis	Aortitis with Aneurysm
I					
II					
III	Normal 8 Abnormal 9 Questionable 4 No EKG 7 Total 28		Abnormal 1		Abnormal 2
IV	Normal 3 Abnormal 4 Questionable 2 Total 9	Abnormal 4 Questionable 1 Total 5	Normal 3 Abnormal 3 No EKG 2 Total 8	Normal 1 Abnormal 1 No EKG 1 Total 3	Questionable 1

Analysis of table 2 shows that no cases of aortitis were diagnosed save in the presence of roentgen-ray abnormalities, although 26 of 57 cases of aortitis showed in addition to roentgen-ray changes definite physical signs of heart disease. Table 2 further shows the frequency of electrocardiographic changes in each of these clinical groups. Uncomplicated aortitis shows electrocardiographic abnormalities less frequently than complicated aortitis, and when present these presumably indicate an associated coronary involvement sufficient to modify the nutrition of the heart muscle, although usually not sufficient to produce characteristic coronary changes.

Electrocardiograms were obtained on 47 of the 57 aortitis cases, and in 24, or 51 per cent, the curves were definitely abnormal, while in eight, or 17 per cent, the curves were considered questionable, making a total of 68 per cent of either abnormal or questionable electrocardiograms in this group of aortitis patients.

ELECTROCARDIOGRAPHIC STUDIES

The criteria employed were those approved by the American Heart Association.[21]

In an earlier publication one of us (C. T. B.)[22] has shown that low voltage of R (not more than 5 to 8 mm.) occurring in Leads I or II "is of sufficient value to be considered in connection with the prognosis of any cardiac case." This standard is less rigid than that of Sprague and White[23] and that of the Committee referred to in the foregoing paragraph. To avoid any criticism as to standards it has seemed preferable in the present study to adhere throughout to the accepted criteria.

The eight questionable abnormal curves (table 2) showed slurred R-waves in two cases, high R-wave in two, low R-wave in one, a questionable coronary S–T in one, slight left axis deviation in two, R-wave inverted in one, and T-wave inverted in one; but while all of these represented deviations from the normal, a conservative reading justified the interpretation of questionably abnormal rather than clearly abnormal electrocardiograms. Approximately 11 per cent, or every ninth, of all our curves fell in this class. In all cases of left axis deviation the habitus of the individual was considered and only those were regarded as abnormal in which the sthenic habitus could be excluded.

An electrocardiogram was obtained in 114 of the 145 paretics studied. Table 3 shows the distribution with reference to physical, roentgen-ray and

TABLE III

To Show the Distribution of 114 Paretic, 20 Tabetic and Tabo-Paretic, and 30 Meningo-Vascular Cases with Reference to Physical, X-Ray, and Electrocardiographic Changes

Electrocardiograms	Physical and X-Ray Examination							
	Group I Normal Physical Normal X-Ray		Group II Abnormal Physical Normal X-Ray		Group III Normal Physical Abnormal X-Ray		Group IV Abnormal Physical Normal X-Ray	
	Number of Cases	Per cent	Number of Cases	Per cent	Number of Cases	Per cent	Number of Cases	Per cent
Paretics (114 cases).....	72	100.0	7	100.0	19	100.0	16	100.0
Normal.....	48	66.7	2	28.5	8	42.1	4	25.0
Abnormal.....	17	23.6	4	57.1	8	42.1	9	56.3
Questionable.....	7	9.7	1	14.3	3	15.8	3	18.7
Abnormal and Questionable.....	24	33.3	5	71.4	11	57.9	12	75.0
Tabo-Paretics and Tabetics (20 cases).....	13	100.0	2	100.0	2	100.0	3	100.0
Normal.....	10	77.0	1	50.0	1	50.0	0	0.0
Abnormal.....	2	15.4	1	50.0	1	50.0	3	100.0
Questionable.....	1	7.6	0	0.0	0	0.0	0	0.0
Abnormal and Questionable.....	3	23.0	1	50.0	1	50.0	3	100.0
Meningo-Vascular (30 cases).....	18	100.0	1	100.0	6	100.0	5	100.0
Normal.....	10	55.6	1	100.0	0	0.0	2	40.0
Abnormal.....	6	33.3	0	0.0	5	83.3	2	40.0
Questionable.....	2	11.1	0	0.0	1	16.7	1	20.0
Abnormal and Questionable.....	8	44.4	0	0.0	6	100.0	3	60.0

electrocardiographic changes in this group of 114 paretics and also shows as follows:

1. 33.3 per cent abnormal or questionable electrocardiograms in paretics Group I.

2. 71.4 per cent abnormal or questionable electrocardiograms in paretics Group II.

3. 57.9 per cent abnormal or questionable electrocardiograms in paretics Group III.

4. 75 per cent abnormal or questionable electrocardiograms in paretics Group IV.

We find that one-third of paretics without physical or roentgen-ray changes show an abnormal electrocardiogram, and this is abnormal much more frequently in the presence of physical, roentgen-ray or combined physical and roentgen-ray abnormalities. Abnormal physical signs appear to be more frequently associated with electrocardiographic changes than are roentgen-ray changes alone.

Twenty tabetics and tabo-paretics were similarly studied and in table 3 we show that in Group I, 23 per cent of the electrocardiograms are abnormal and, as in the paretic Groups II, III and IV, show a marked increase in the incidence of electrocardiographic abnormalities. Thirty meningo-vascular cases show 44.4 per cent electrocardiographic abnormalities in Group I. As in the paretics, tabetics and tabo-paretics an increase in electrocardiographic abnormalities is noted in the other groups, especially Group III, which shows practically 100 per cent abnormalities.

Especial interest attaches to the question as to what per cent of these cases, which were clinically normal from the cardiovascular standpoint, will show electrocardiographic abnormalities.

Table 4 shows 103 cases of central nervous system syphilis which on physical and roentgen-ray examination we considered normal from the cardiac standpoint.

TABLE IV

To Show the Incidence of Electrocardiographic Changes in Group I (Normal Physical and Normal X-Ray) in 72 Paretic, 13 Tabo-Paretic and Tabetic, and 18 Meningo-Vascular Cases

Electrocardiogram	Group I Paretic Normal Physical Normal X-Ray	Group I Tabetic and Tabo-Paretic Normal Physical Normal X-Ray	Group I Meningo-Vascular Normal Physical Normal X-Ray
Normal EKG:			
Number of cases	48	10	10
Per cent of cases	66.7%	76.9%	55.5%
Abnormal EKG:			
Number of cases	17	2	6
Per cent of cases	23.6%	15.4%	33.3%
Questionable EKG:			
Number of cases	7	1	2
Per cent of cases	9.7%	7.6%	11.1%
Abnormal and Questionable EKG:			
Number of cases	24	3	8
Per cent of cases	33.3%	23%	44.4%
Totals	72	13	18

Of the 72 paretics, 33.3 per cent showed abnormal or questionable electrocardiograms.

Of the 13 tabo-paretics and tabetics, 23 per cent showed abnormal or questionable electrocardiograms.

Of the 18 meningo-vascular cases, 44.4 per cent showed abnormal or questionable electrocardiograms.

While the number of meningo-vascular cases is small as compared to that of the paretics the high percentage of electrocardiographic abnormalities is striking and suggests that the selective affinity of the spirochete for certain tissues discussed earlier in this paper may well explain this increased frequency of electrocardiographic abnormalities as compared with the paretic group.

Summary of Electrocardiographic Findings

Of 215 syphilitic cases, electrocardiograms were obtained in 164 and were abnormal or questionable in 47 per cent. Of 100 hospital control cases electrocardiograms were obtained on 100, and were abnormal in 33 per cent. Many of these changes were slight—especially in the control group—and included axis deviation and departures from the normal which could hardly be considered significant. Furthermore, in the syphilitic group multiple changes and changes involving all leads were much more frequent.

Our hospital control series consists of a group of 100 consecutive Psychopathic Hospital patients (average age 40 years) in whom there was no evidence of syphilis. Seven of these showed physical evidence of heart disease—a much higher incidence than in the general population. Therefore, we considered this an unsatisfactory control and planned a further control series. There were, however, no roentgen-ray changes in this control group. The high incidence of electrocardiographic abnormalities in these hospital patients is probably accounted for by the fact that they had undergone cardiac changes which would not be encountered in a control group of normal individuals.

Since this control series of hospital patients appeared in some respects to be unsatisfactory, we studied a second control series of individuals who were theoretically normal, although not comparable as to age.

One hundred medical students of an average age of 26 years (the extreme ages being 21 and 42) were submitted to physical, roentgen-ray and electrocardiographic examinations. Of these, 94 furnished normal electrocardiograms employing the same standards as have been mentioned in the preceding text. Eighty-five of these showing normal electrocardiograms were found normal on physical and roentgen-ray investigation, five showed physical abnormalities but normal roentgen-rays, and four presented physical or roentgen-ray abnormalities, but none of these was considered indicative of heart disease. In two fibroid phthisis was the

cause of cardiac displacement. Of the group of five showing abnormal physical signs a definite cardiac diagnosis was made in three cases, in one mitral stenosis and insufficiency, and in two mitral insufficiency; but in the remaining two faint systolic murmurs at the apex, not transmitted, were the sole abnormalities and probably were of functional origin. Of this group of 100 students there was therefore an incidence of clinical cardiac pathology of 3 per cent—a percentage in line with accepted standards.

In the interpretation of the teleroentgenograms the small, the " asthenic " or the " drop " heart, the transverse heart and very slight right displacement, in the absence of other roentgen-ray or clinical evidence, were classed as normal.

Of the 100 controls in this series only six showed abnormal electrocardiograms, but all of these appeared normal on physical and roentgen-ray examination. In this connection it is interesting to note that the three individuals in whom a definite cardiac diagnosis could be made showed normal curves.

In six of the 100 controls the electrocardiograms were considered abnormal. In two there was abnormal right axis deviation without other change in the QRS complex, in one there was abnormal left axis deviation, in one abnormal left axis deviation with other changes in the QRS complex, in one T_{1+2} were low and T_3 inverted, and in one there was low voltage of the R-wave in all leads.

The abnormalities noted in the six controls showing abnormal electrocardiograms are summarized as follows:

Abnormal right axis deviation without other QRS changes	2
Abnormal left axis deviation without other QRS changes	1
Abnormal left axis deviation with other QRS changes	1
Low voltage of R_{1+2+3}	1
Low voltage of T_{1+2} with T_3 inverted	1
Total	6

Table 5 furnishes a comparison of the significant electrocardiographic findings in our patients falling in Group I and those of our two control series. Ninety-three of the hospital control series would likewise fall in Group I since only seven of the 100 hospital control patients showed physical evidence of heart disease, and none of them roentgen-ray abnormalities. Likewise 97 of our student control may be considered as comparable to Group I, since in all others showing abnormalities the physical or roentgen-ray findings were not considered to indicate heart disease. We show that *R-S-T wave abnormalities, usually associated with coronary and myocardial changes, occur much more frequently in the syphilitic group, and that the coronary S-T curve occurs exclusively in this group* (9 cases). Because of multiple changes found in a single electrocardiogram, percentage comparisons as to the foregoing changes are confusing and therefore omitted. Axis deviation was of no value in diagnosis.

TABLE V

Electrocardiographic Findings in Group I (Physical and X-Ray Findings Normal) on 103 Cases of Central Nervous System Syphilis as Compared with Control Groups

Electrocardiographic Findings	Central Nervous System Syphilis			Controls 93 Hospital Cases	Controls 97 Medical Students
R-wave low			8	5	2
R-wave slurred in Leads I or II			12	8	2
T-wave changes significant *	High	7	22	4	0
	Low	11			
	Inverted	4			
Coronary changes **	Unquestionable	6	9	0	0
	Probable	3			

* High T-wave or T-wave inverted.
** Includes Pardee curve.

We find that the greatest percentage of electrocardiographic changes occurs a decade earlier (fourth decade) in our syphilitic group than in the hospital control group of comparable age, suggesting an earlier cardiac involvement in syphilis.

Leary and Wearn [24] have stressed the infrequency of coronary as compared to cerebral involvement in syphilis and suggest that where there is coronary closure, an adequate myocardial circulation may be maintained by means of the Thebesian veins, first demonstrated as far back as 1706. Pratt [25] likewise in 1898 showed the possibility of a blood supply from the ventricles directly to the heart muscle. We show a significant incidence of coronary involvement. The fact that many of these patients failed to present symptomatic evidence may be explained on the foregoing basis.

The percentage of abnormal electrocardiograms is higher in the syphilitic group (47 per cent) than in the hospital control group (33 per cent), and because of this high percentage in the control group we have presented a student control group showing only 6 per cent of abnormal electrocardiograms. Yet there was no significant change noted in the syphilitic group which was not found in the hospital control group with the sole exception of the coronary S–T change found in nine cases. It thus appears that while electrocardiographic changes occur in greater frequency in syphilis than in a control group of comparable non-syphilitic individuals, there is nothing sufficiently characteristic in the electrocardiograms of these patients to be of more than confirmative evidence when considered in association with the clinical findings in the case; but there will often occur evidence of coronary and myocardial change in the heart of the syphilitic patient not demonstrable by other than graphic means. The electrocardiogram is therefore of considerable value in the diagnosis and subsequent management of the patient.

Pathologic Studies

Thirty-three patients died and autopsies were obtained on 14 or 42 per cent.

Table 6 shows that in Case 4726 a definite syphilitic aortitis was not diagnosed. In Case 5016 the evidence was not so clear, but the pathologist after considerable study classified this as syphilitic aortitis, likewise not

Table VI

Relation Between Physical Changes and Aortic Changes as Disclosed by Microscopic Findings

Hospital Number	Age	Duration of Symptoms (Chancre)	Physical Findings	Microscopic Condition of the Aorta
3360	48	28 years	Negative	No evidence of syphilis.
3921	53	?	Negative	No evidence of syphilis.
5067	27	10 years	Negative	No evidence of syphilis.
3316	48	10 years	Negative	No evidence of syphilis.
3654	40	12 years	Negative	No evidence of syphilis.
4113	26	4 years	Negative	No evidence of syphilis.
4699	53	?	Negative	No evidence of syphilis.
3599	49	30 years	Negative	Some lymphocytic infiltration in adventitia. No definite evidence of syphilis, but suspicious.
5016	65	20 years	Negative	Marked lymphocytic infiltration of adventitia. Patches of necrosis of media. Fibrosis of intima. Syphilitic aortitis.
4726	39	?	Negative	Syphilitic aortitis.
5146	58	31 years	Aortitis, hypertrophy, hypertensive heart disease.	Syphilis of aorta and aortic valves.
4184	61	?	Aortitis with aortic insufficiency.	Syphilis of the aorta.
5496	48	25 years	Aortitis.	Suggestive changes indicative of syphilitic aortitis.
4376	55	?	Aortitis, hypertension, myocardial insufficiency.	Syphilitic aortitis.

diagnosed ante mortem. In the remaining 12 cases the antemortem diagnosis was confirmed.

Change in the Electrocardiogram after Malarial Treatment

The literature presents occasional cases of sudden death in the course of malarial treatment of paresis—in the absence of clinical evidence of heart involvement. Bach and Worster-Drought,[26] discussing this, state that at autopsy invariably aortitis or myocarditis was found. We find no reports in the literature of electrocardiographic studies of these cases, but Mikawa [27] and his associates studied the effect upon the electrocardiogram in patients inoculated with malaria in the treatment of gonorrhea. They showed some amplitude changes, especially in the S-wave in the course of the fever, and a transient conduction disturbance, but failed to state the duration of this disturbance. Thirty-nine of our malarial treatment cases had electrocardiograms before and after treatment; there was no change

in 54 per cent, a slight change in 28 per cent and a definite change in 18 per cent, but the duration and meaning of this change has not been determined.

This is a very small group of cases but, excepting Mikawa's studies which were on six patients only, we appear to present the only existing information on the subject.

Slight shift of the axis to the right after treatment was observed five times, was unchanged twice and disappeared in one instance. Thus in eight of 18 cases there was slight axis shifting, usually to the left. T-wave changes, especially in Leads II and III, either a tendency to flattening of the wave or inversion of the wave, were the only other changes at all frequent. Some change in the T-wave occurred in seven cases. Certainly this group is too small to justify any conclusions drawn from the foregoing observations.

We have not attempted in this paper any consideration of the effects of treatment upon established cardiovascular syphilis, but will record the observation that two cases, 8 and 11, showed a significant diminution in size of the aorta following malarial treatment.

The Effect of Treatment upon the Incubation Period of Neurosyphilis

Considerable controversy is current as to the merits of early treatment of syphilis, especially the use of arsphenamine. Wilmanns and Steiner [29] hold that this treatment predisposes the syphilitic patient to the development of parenchymatous neurosyphilis, while Smith and Frankl [30] do not concur in this viewpoint. German and French workers [31] have shown that the treatment of early syphilis has shortened the period of incubation in parenchymatous neurosyphilis whether treated with mercury or arsphenamine. Moore and Hopkins [32] report that adequate and proper treatment of late nonsymptomatic neurosyphilis will prevent the development of clinical neurosyphilis. Hopkins [28] has pointed out that "inadequate treatment of early or late syphilis shortens the incubation period not only of tabes and dementia paralytica, but also of late meningo-vascular neurosyphilis." In this paper the term incubation period is used to denote the period elapsing between the primary lesion and the appearance of symptoms of neurosyphilis.

It is interesting to note that in this group of 215 proved cases of central nervous system syphilis only 72, or 30 per cent, gave a history of a chancre; of these 72, only 22 gave a history of some form of therapy.

In each case which gave a definite history of treatment we have attempted to gain a full history of the nature of such treatment. While in some few cases this was unsatisfactory, we feel that the majority of cases have related a complete history of their treatment. In none of these was the luetic condition adequately treated according to present day accepted

standards. In keeping with this, we submit the following statement taken from one of the cases which is fairly typical:

Chancre contracted in 1907, while in the Navy. Treated in Naval Hospital in Brooklyn, given calomel and potash for a period of two months. No further treatment until 1922: took four courses of four treatments each. In 1928 took four treatments of neosalvarsan. Some iodine was also taken at that time. In January and March 1930, took six treatments of neosalvarsan, also had two Swift-Ellis treatments.

With the past and present emphasis placed upon the need of early and adequate treatment of syphilis it is surprising that in our series only 10.2 per cent of the cases were treated, whereas Hopkins [28] reports 43 per cent.

In Table 7 we present evidence to show that inadequate treatment of

TABLE VII

The Influence of Inadequate Treatment Upon Incubation Period of 72 Cases of Neurosyphilis

	Paretics		Tabo-Paretics		Tabetics		Meningo-Vasculars	
	Cases	Period of Incubation	Cases	Period of Incubation	Cases	Period of Incubation	Cases	Period of Incubation
Cases not treated.	29	16.97 years	4	22.10 years	6	20.30 years	11	14.30 years
Cases inadequately treated.....	14	14.20 years	0		4	10.50 years	4	7.90 years
Total number of cases.....	43		4		10		15	
Incubation period shortened.....		2.77 years				9.8 years		6.4 years

early and late syphilis shortens the period of incubation of paresis, tabes dorsalis, and meningo-vascular syphilis. In paresis this amounted to 2.77 years on the basis of 43 cases, in tabes dorsalis 9.8 years on the basis of 10 cases, and in meningo-vascular syphilis 6.4 years on the basis of 15 cases.

THE EFFECT OF TREATMENT UPON THE TIME OF APPEARANCE OF SIGNS OF HEART INVOLVEMENT

We have also studied these cases from the standpoint of their cardiac changes. The results are presented in table 8. Of the 50 untreated cases, 22 per cent were found to be abnormal on physical and roentgen-ray examination, while of the 22 inadequately treated cases 41 per cent were abnormal —that is, cardiac changes demonstrable by physical and roentgen-ray means were found approximately twice as often in the inadequately treated cases as in the untreated cases. On the basis of 57 electrocardiograms performed on the 72 patients giving a history of syphilis, abnormal curves occurred more frequently in the inadequately treated group than in the non-treated group, although not to the same extent as above.

Emphasis should be placed upon the potential danger of inadequate treatment in early and late syphilis as such treatment apparently interferes

TABLE VIII

The Contrast of Inadequate Treatment and No Treatment as Shown by Physical, X-Ray, and Electrocardiographic Changes

Groups	Non-Treated Cases		Inadequately Treated Cases	
	Number	Per Cent	Number	Per Cent
I Normal Physical and X-Ray	39	78	13	59
II, III, IV—Either Abnormal Physical or X-Ray or Both	11	22	9	41
Totals:	50	100	22	100
Normal Electrocardiogram	24	60	8	47
Abnormal Electrocardiogram	16	40	9	53
Totals:	40	100	17	100

with the resistance-building mechanism of the body and predisposes the patient not only to the development of neurosyphilis but of cardiac syphilis as well. At the present time we do not have sufficient data to report the incidence of neurosyphilis in adequately treated early cases of syphilis. Incomplete data indicate that the incidence is very low.

SUMMARY AND CONCLUSIONS

We have intensively studied a group of 215 cases of neurosyphilis in order to determine the frequency and type of cardiovascular involvement.

1. We find that 73, or 33.9 per cent, show some form of cardiovascular pathology, independent of the electrocardiogram.

2. Our findings are in agreement with others as to the importance of aortitis in syphilis, it furnishing the most frequent type of cardiovascular pathology in syphilis.

3. In association with syphilitic aortitis we find electrocardiographic abnormalities in 68 per cent of our cases.

4. 33.3 per cent of our paretics, 23 per cent of our tabo-paretics and tabetics, and 44.4 per cent of our meningo-vascular cases, without physical or roentgen-ray abnormalities of the heart, showed abnormal electrocardiograms; and the electrocardiogram was abnormal in a much higher proportion in the presence of physical, roentgen-ray or combined physical and roentgen-ray abnormalities. Abnormal physical signs appear to be more frequently associated with electrocardiographic changes than are roentgen-ray changes alone.

5. We find a significant increase in electrocardiographic abnormalities in neurosyphilis, but no change which can be considered as characteristic of cardiovascular syphilis, although we are impressed with the incidence of coronary changes in our series.

6. The incidence of electrocardiographic abnormalities not associated with physical or roentgen-ray changes noted in this series of neurosyphilitics

justifies the routine use of the electrocardiogram in these cases as a means of an earlier recognition of cardiovascular involvement.

7. The incubation period of neurosyphilis is shortened in paretics, tabetics, and meningo-vascular cases who have received early or late, but inadequate treatment.

8. Cardiac lesions seem to be found more frequently in those cases inadequately treated. This is demonstrable by either physical, roentgen-ray, or electrocardiographic changes.

9. There is definite need for more adequate therapeutic procedures in early and late syphilis to decrease the incidence of neurosyphilis.

BIBLIOGRAPHY

1. Coombs, C. F.: Syphilis of heart and great vessels (Lumleian lecture), Lancet, 1930, ii, 227–231, 281–286, 333–338.
2. Moore, J. E., Danglade, J. H., and Reisinger, J. C.: Treatment of cardiovascular syphilis, results obtained in 53 patients with aortic aneurysm and in 112 with aortic regurgitation, Arch. Int. Med., 1932, xlix, 879–924.
3. Moore, J. E., Danglade, J. H., and Reisinger, J. C.: Diagnosis of syphilitic aortitis uncomplicated by aortic regurgitation or aneurysm, comparison of clinical and necropsy observations in 105 patients, Arch. Int. Med., 1932, xlix, 753–766.
4. Warthin, A. S.: Primary tissue lesions in the heart produced by *Spirochete pallida*, Am. Jr. Med. Sci., 1914, cxlvii, 667–672.
5. Warthin, A. S.: Sudden death due to exacerbation of latent syphilitic myocarditis, Am. Heart Jr., 1925, i, 1–24.
6. Warthin, A. S.: The rôle of syphilis in the etiology of angina pectoris, coronary arteriosclerosis and thrombosis, and of sudden cardiac death, Ann. Int. Med., 1931, iv, 1347–1351.
7. Friedman, E. D.: The associated incidence of syphilis of the central nervous system and cardiovascular syphilis, Arch. Neurol. and Psychiat., 1919, i, 289–300.
8. Lendon, G.: Syphilis of heart and great vessels, Med. Jr. Australia, 1932, ii, 41–46.
9. Jagic, N.: Clinical characteristics and treatment of syphilitic mesaortitis, Wien. klin. Wchnschr., 1928, xli, 845–847.
10. Turner, K. B., and White, P. D.: The heart and aorta in early syphilis, clinical observations, Arch. Int. Med., 1927, xxxix, 1–11.
11. Brooks, H.: Heart in syphilis, Am. Jr. Med. Sci., 1913, cxlvi, 513–531.
12. Brooks, H.: Syphilis of the heart, Am. Jr. Syph., 1921, v, 217–247.
13. Moore, W. C.: Cardiac syphilis, Am. Jr. Med. Sci., 1918, clv, 660–668.
14. Wile, U. J., and Marshall, C. H.: A study of spinal fluid in 1869 cases of syphilis in all stages, Arch. Dermat. and Syph., 1921, iii, 272–278.
15. Lucke, B., and Rea, M. H.: Studies on aneurysm, Jr. Am. Med. Assoc., 1921, lxxvii, 935–940.
16. Musser, J. H., Jr., and Bennett, A. E.: Incidence of syphilis of aorta with interstitial and parenchymatous neurosyphilis, Arch. Int. Med., 1924, xxxiv, 833–840.
17. Riven, S. S., and Feigenbaum, J.: Syphilis of the aorta and heart, clinical study, Canad. Med. Assoc. Jr., 1930, xxiii, 656–660.
18. White, P. D.: Diagnosis of cardiovascular syphilis, New England Jr. Med., 1933, ccviii, 179–184.
19. Coombs, C. F.: Diagnosis and treatment of syphilis of aorta and heart, Quart. Jr. Med., 1932, i, 179–211.
20. Kurtz, C. M., and Eyster, J. A. E.: Fluoroscopic studies of heart and aorta in acquired and congenital syphilis, Am. Heart Jr., 1930, vi, 67–76.

21. Criteria for the classification and diagnosis of heart disease, third edition, 1932, New York Tuberculosis and Health Association, New York.
22. BURNETT, C. T., and PILTZ, C. F.: Low voltage in the electrocardiogram, Am. Heart Jr., 1927, ii, 649–654.
23. SPRAGUE, H. B., and WHITE, P. D.: The significance of electrocardiograms of low voltage, Jr. Clin. Invest., 1926, iii, 109–121.
24. LEARY, T., and WEARN, J. T.: Two cases of complete occlusion of both coronary orifices, Am. Heart Jr., 1930, v, 412–423.
25. PRATT, F. H.: Nutrition of heart through vessels of Thebesius and the coronary veins, Am. Jr. Physiol., 1898, i, 86–103.
26. BACH, F., and WORSTER-DROUGHT, C.: Interrelation of neurosyphilis and cardiovascular syphilis, Lancet, 1930, ii, 1113–1115.
27. MIKAWA, T., NOMURA, G., and HARADA, N.: Electrocardiogram of patients inoculated with malaria, Acta scholae med. univ. imp., Kioto, 1929, xi, 391–401.
28. HOPKINS, H. H.: Incubation period of clinical neurosyphilis, Arch. Neurol. and Psychiat., 1933, xxix, 158–161.
29. WILMANNS, K., and STEINER, G.: Syphilis und metasyphilis, Ztschr. f. d. ges. Neur. u. Psych., 1926, ci, 875–916.
30. SMITH, J. C.: Notes on the appearance of dementia paralytica and the relation between its frequency and the antisyphilitic treatment, Acta psych. et neur., 1926, i, 346–359.
FRANKL, S.: Der Einfluss therapeutischer Massnahmen auf das Auftreten von Tabes und Paralyse, München. med. Wchnschr., 1930, lxxvii, 1879–1881.
31. JAGDHOLD, H.: Über die Beziehungen der spezifischen antiluischen Behandlung zum Entstehen der Metalues, Ztschr. f. d. ges. Neur. u. Psych., 1930, cxxviii, 151–171.
SEZARY, A., and ROUDINESCO: L'incubation du tabes et de la paralysie générale, Bull. et mém. Soc. méd. d. hôp. de Paris, 1931, xlvii, 968–977.
32. MOORE, J. E., and HOPKINS, H. H.: Asymptomatic neurosyphilis; prognosis of early and late asymptomatic neurosyphilis, Jr. Am. Med. Assoc., 1930, xcv, 1637–1641.

ABDOMINAL PAIN: ITS SIGNIFICANCE AND DIAGNOSTIC VALUE*

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THE diagnosis of intra-abdominal pathology is extremely difficult. We have no method for exact diagnosis such as the electrocardiogram for the cardiac lesion, the blood in primary anemias, the urine and functional studies in the nephritides and the sputum in pulmonary tuberculosis. We are helped a little in making such diagnoses by the study of gastric and duodenal contents, more by study of the stool, much more by fluoroscopy and radiography of the digestive tract. The physical examination of the abdomen is of course essential; often, however, in its interpretation puzzling and indefinite. Therefore, in many cases, in making a definite or potential diagnosis, we must depend upon the analysis and interpretation of the symptoms, the history of the case, its beginning, its evolution; upon our proper interpretation of these our final diagnosis often depends.

Few of these symptoms are diagnostic in themselves; for example, constipation may simply represent faulty habits of eating and living and be purely functional, but it may be the first sign of a colonic neoplasm or of some extra-gastrointestinal disease as, for example, unsuspected hypothyroidism; while an intractable diarrhea, usually of gastrogenous or enterogenous origin, may be the first and only symptom of the opposite condition—hyperthyroidism. Nausea, distress and vomiting may be of gastric or intestinal origin, but it may also represent the main symptoms of cardiac or renal disease, of gall-bladder pathology, or may be purely psychogenic—the mirror of a disturbed mind or the expression of maladjustment to the environment. But the symptom which most frequently brings the patient to the doctor, the symptom whose correct interpretation is most important in helping us to a correct diagnosis, is pain.

The cause of superficial pain is simple and easy to understand—specific pain nerves with exquisite localizing powers furnish a protective mechanism to external trauma and are essential to the preservation of the individual and the evolution of the race. The cause of visceral pain is not simple and is not easily explained. There are no such specific pain nerves as are met with in the skin and no need for them as the viscera are protected against external trauma by the bony and muscular cage which encloses them. The normal physiology of digestion proceeds automatically and autonomically. Health is spelt by a proper balance between two opposing sets of impulses—one stimulating, one inhibiting; pain or discomfort probably represents lack of balance in this mechanism, usually secondary to organic pathology in the viscera themselves. And thus, what we interpret as pain, in reality probably represents change in intra-gastric or intra-intestinal pressure, increased tonus, or hyperactive peristalsis.

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Most investigators feel that there are few, if any, true pain fibers in the nerves supplying the abdominal organs. We know, for instance, that the viscera can be crushed or burnt or pressed upon with great force without any pain, though Langley and Gaskell believe that there are a few medullated sensory fibers in the splanchnics. These must be very few, if any, because of the obvious lack of sensation of the viscera in the ordinary sense and the extreme paucity of the afferent fibers in the nerves supplying the abdominal organs. We know that the visceral peritoneum is devoid of pain fibers. Capps believes that true sensory fibers may exist in the parietal peritoneum which may give rise to pain and to some extent localize it; but most physiologists think that in the parietal, as in the visceral, peritoneum there are no true pain fibers and that discomfort or pain produced by pressure is brought about by sensations arising from the rich nerve supply of the loose connective tissue external to the parietal peritoneum.

Certainly the weight of evidence is in favor of the view that there is almost complete absence of true pain receptors in the visceral walls. Many physiologists believe that hypertonus, increased pressure, and overactive peristalsis are the causes of so-called abdominal pain, that impulses may arise in afferent nerve endings of the viscera as a result of stretching or compression, that this pain is not localized but is usually referred to certain areas in the surface of the body and may be associated with superficial or even somewhat deeper sensitiveness of the cutaneous and muscular covering. But this explanation, while fairly satisfactory as regards the intestine, is not enough to explain the pain met with in certain other portions of the abdomen, notably the stomach. Here we must presuppose that the disease produces a very definite hypersensitiveness; possibly the development of irritable foci in certain regions of the spinal cord due to repeated abdominal impulses; possibly a local hypersensitiveness to any form of stimuli at the seat of the lesion itself as well.

Thus, in our analysis of the causes of abdominal pain, perhaps our best explanation is that abdominal impulses may result in referred pain—the viscerosensory reflexes—tenderness, that is cutaneous or muscular hyperalgesia; muscular contractions, that is muscle spasm or *défense musculaire*. Possibly certain sensations are due to a lowered threshold of pain or to hypersensitiveness in the lesion itself or in that area of the spinal cord connected with the lesion through its nerve supply.

Thus, abdominal pain is a very complex phenomenon and its interpretation may be made difficult by many confusing factors: the similarity of the nerve supply to many of the abdominal viscera as well as to certain contiguous organs such as the heart and lungs, the diversity of the paths through which painful sensations may leave the abdomen, the proximity of the visceral organs to each other—one's hand can almost cover gall-bladder, pylorus, duodenum and a segment of the transverse colon, while the thin diaphragm alone separates heart and lungs from liver, stomach and spleen. Perhaps an even more difficult factor in the interpretation of pain is the

enormous variation in the picture due to individual variation in response to stimuli.

In analyzing and interpreting abdominal pain, we have to consider all of these factors—physiological imbalance, organic pathology; congenital or acquired, local or general hypersensitiveness; the overlapping and confusion of symptoms due to similar nerve supply and close proximity of organs; the whole modified to a tremendous degree by the emotional stability or instability of the patient.

At the present time, this last factor has been given perhaps undue prominence. It is the fashion of the age to explain complaints on a purely psychogenic basis—emotional instability, lack of insight, maladjustment—and to advise a treatment based upon such a conception—reëducation, psychotherapy, the removal or minimization of psychic strain. This is a dangerous attitude of the mind as regards abdominal pain, for while minor discomfort may be exaggerated into exquisite pain by the neurotic, and all forms of pain may be simulated by the auto- or hetero-suggestion of the hysterical, these are usually recognized and properly interpreted by the competent physician. True abdominal pain usually means organic pathology and its underlying basis is usually structural change. It is a very dangerous thing to diagnose gastralgia or enteralgia and to ascribe to a psychasthenic state symptoms associated with true pain, especially if associated with rise of temperature, with local tenderness, with an increased leukocyte count. Too often such an interpretation will lead to deplorable delay and the appendix ruptures or an ulcer perforates while the patient is being treated on the assumption that the condition was purely functional.

In the interpretation of pain, its evolution, its localization, its radiation, its character, its constancy or its irregularity, its periodicity, there are certain general principles which one should never forget. First, that the pain is a summation of local pathology, organic or functional, and psychic response; thus a mild lesion in a psychasthenic individual may elicit much more complaint than a far more serious lesion in a stable person. Second, the size or extent of the lesion has absolutely no relation to the severity of the pain. A pin point erosion of the mucous membrane can produce as much pain as a deep callous ulcer; a small gall-stone usually gives much more pain than a large one; a gastric ulcer and even a duodenal ulcer may give no pain whatsoever; pain is absent in many cases of cancer of the stomach. It is the tragedy of cancer that pain is not an early symptom, often not even a late symptom; when it appears it usually represents the beginning of obstructive symptoms rather than anything integral to the growth of the cancer itself. Third, while the disappearance of pain usually means improvement, sometimes the reverse is true, as in a gangrenous appendix or gall-bladder.

There are certain pain patterns which we should never forget and which are almost diagnostic—pictures which give us our probable diagnosis from the history of the patient alone. Such is the pain of duodenal ulcer, with its relief by food, its periodicity, and its punctuality. Moynihan used to

say he could set his watch by the hunger pains of his patients, while as regards its periodicity, we all know that spring and fall are the times of election. Such also are the agonizing attacks of upper right quadrant colic with radiation to the right shoulder, so often met with in cholelithiasis and peculiarly likely to occur during the wee small hours of the night; the discomfort or cramp-like pain, beginning in the epigastrium and finally localizing in the lower right quadrant, of acute appendicitis, with its local tenderness, its muscle spasm, its constipation, nausea, fever and increased leukocyte count; the agonizing pain with circulatory collapse of acute pancreatitis and the somewhat similar picture of perforated ulcer with absence of early collapse; the periodic cramp-like pains due to intestinal obstruction, whatever its cause.

These are clearcut clinical pictures, where the location of the pain, the type of pain, the history of the pain, often without the associated clinical and laboratory findings, give us as a rule a definite diagnosis. But we must never forget that each one of these can be simulated by intra- or even extra-abdominal conditions in a certain small proportion of cases. Renal colic may absolutely simulate biliary colic; duodenal ulcer may occasionally give the picture of a gall-stone attack; while ulcer, gall-bladder disease or appendiceal disease may be simulated by a great number of other conditions which we will briefly touch upon later also. Every one of these conditions, which as a rule have such characteristic histories, may in certain instances have no local symptoms whatsoever, only symptoms referred elsewhere. For instance, in acute appendicitis, the pain may persist in the epigastric region, it may be only umbilical in location—this in about 5 per cent of the cases; it may simulate a gall-bladder attack or may produce pain only in the back or in the pelvic region or down the right leg.

In many other abdominal conditions, the pain picture or pattern may be suggestive, but not diagnostic. It is blurred, it is confused, as for instance in many cases of gastric ulcer; in a small number of cases of duodenal ulcer, in a larger number of cases of biliary tract disease, and in a considerable number of cases of intestinal obstruction due to neoplasm, postoperative adhesions, etc., where the symptoms are too often explained on a purely functional basis and operation often delayed far too long, especially in the malignant type of obstruction. The diagnosis of chronic appendicitis is unquestionably erroneous in the majority of cases, but it is justified in a small percentage of cases where the pathologic signs are in the lower right quadrant and the referred pain usually in the epigastrium though occasionally in the upper left quadrant.

We have not time, of course, to discuss in detail the many other intra-abdominal conditions where the pain is referred elsewhere in the abdomen or the innumerable cases of disease outside the abdominal cavity where one of the symptoms, sometimes the main symptom, occasionally the only symptom, is abdominal pain, but I do wish to mention certain of these that have

been singularly interesting to us in our very intensive study of abdominal pain over a long period of years.

Let us first discuss briefly certain of the more puzzling examples of referred abdominal pain.

True angina pectoris may present no symptoms above the diaphragm, only violent epigastric pain, without radiation. This unfortunately is only too often diagnosed as an acute indigestion and treated by purgatives and exercise, when morphia and rest may be the only means of saving life. Also a few cases of coronary thrombosis so exactly simulate gall-stone colic that gall-bladders, usually quite normal, have been removed on this false hypothesis. It is well to remember that in a very few instances the reverse of this picture is true—that is, unsuspected gall-bladder disease may present symptoms absolutely simulating attacks of stenocardia or coronary thrombosis. It is also well to remember that rare cases of carcinoma of the liver, and, somewhat more frequently, cases of hepatic cirrhosis may present, during their course, attacks absolutely simulating gall-stone colic, frequently incorrectly confirmed by Graham gall-bladder pictures. In reality the attacks represent no disease of the gall-bladder but acute infections or reinfections of the previously diseased liver.

Perhaps the best explanation of this correlation between cardiac and biliary phenomena is that given by Head: "When a painful stimulus is applied to a part of low sensibility in close central connection with a part of much higher sensibility, the pain is felt in the part of higher sensibility rather than in that of lower sensibility to which the stimulus is actually applied."

This also may be the explanation of the acute abdomen often simulating appendicitis which is met with occasionally in central pneumonia and diaphragmatic pleurisy.

While in many cases the peptic ulcer syndrome may require for its explanation a local hypersensitiveness to irritants, such as acid, or a general or central hypersensitiveness so often associated with emotional crises or psychic strain, nevertheless the bulk of the evidence favors the view that pyloric spasm, increased intragastric pressure, hypertonus and hyperperistalsis play the major rôle in its production. These motor disturbances can be produced so easily by referred impulses from disease elsewhere that it is not surprising that ulcer is often diagnosed in disease of many other organs. For example, in tabes dorsalis, where an Argyll Robertson pupil and absent knee jerks should have given us our clue, although unfortunately it is not infrequent that this clue is overlooked and even surgical treatment employed; in renal or urinary calculus where the urinary findings and a flat plate of the abdomen should have given us our diagnosis; in certain cases of gall-bladder disease where x-ray plates by the Graham method may help us; or in obstruction of the colon, whether benign or malignant, where there are no local symptoms, only those referred to the stomach. Of course in carcinoma of the colon or in obstruction due to other causes, this is not

the usual picture, and the pain, while not definitely localized, is usually in the lower abdomen, usually spasmodic, often with surprisingly long intervals between attacks, and generally misinterpreted for a long period of time. In reality everyone presenting such a syndrome should make us suspect early malignancy, especially in older people, and should set in motion that set of diagnostic procedures—palpation of the abdomen in a hot bath, fluoroscope of the colon by the barium enema, digital rectal examination, study of the stool for occult blood—that should either confirm or refute this suspicion.

A small epigastric hernia may produce pain absolutely similar to that of ulcer, and the same may be true of herpes zoster before the appearance of the eruption, although here, as a rule, the pain is much more likely to simulate acute appendicitis. Lower right quadrant pain simulating subacute or chronic appendicitis is met with in such a varied group of diseases elsewhere that it would be remarkable if incorrect diagnoses were not singularly likely to occur with this syndrome. Right-sided pyelitis, especially in young female children where the urine may be clear due to the plugging of the ureter on the infected side, true ureteral stricture (a rare condition), right salpingitis, ovarian cyst with twisted pedicle and tubal pregnancy, all present pictures suggestive of appendicitis, but usually differentiated by careful examination.

Perhaps equally interesting and certainly more puzzling is the picture suggesting an acutely diseased appendix met with in certain of the infectious diseases—notably measles before the appearance of the eruption, typhoid fever in its early stage, acute follicular tonsillitis, influenza, in a few instances even scarlet fever and undulant fever, the latter showing a peculiarly puzzling picture when it has mainly abdominal manifestations. Perhaps the best explanation in many of these cases is a marked localization of the infectious agent in the rich lymphoid tissue about the cecum. In this connection, we know that tuberculous or nontuberculous adenitis, localized in this area, may absolutely simulate appendicitis; while allergic phenomena, such as we meet with in angioneurotic edema or in Henoch's purpura, may present a similar lower right quadrant picture. Perhaps the most difficult of all to explain is the acute abdomen, usually simulating acute appendicitis, sometimes found in sickle cell anemia.

Space does not permit us to call attention to other rare causes of abdominal pain with which we have met. Each of these presents its own special problem, where a correct diagnosis is often singularly difficult, sometimes impossible, as for instance, chronic pancreatitis in the aged, a much neglected diagnosis, with epigastric pain, usually mild; the puzzling abdominal pain of arthritis of the spine; of aneurysm of the renal artery; of a psoas abscess or of a burrowing abscess secondary to a diverticulitis; of tuberculosis of the mesenteric or retroperitoneal glands; of an unsuspected localized osteomyelitis; mesenteric thrombosis; atypical ileus and chronic intussusception.

Each of these presents its individual problem, but in most cases this is capable of solution if the diagnostic procedure is thorough and the reasoning of the clinician logical.

In the solution of each of these abdominal problems, we must of course utilize every diagnostic procedure. We must take a careful and complete history, make a thorough physical examination, and utilize to the full the findings from the clinical and x-ray laboratories, but in almost every case, the pain picture is a valuable, often an invaluable, aid; while sometimes it is the only key that will unlock the closed door.

True clinical research is far more difficult than laboratory investigation, but if done scientifically and thoroughly by one who knows the art, as well as the science, of medicine, it is equally productive of results. In clinical research there is no more promising field than that of the interpretation of abdominal pain. It is a very difficult field—the picture often blurred, pain patterns overlapping because we are not analyzing pictures produced by true visceral pain fibers but are trying to interpret physiological dysfunction.

Sometimes the problem is insoluble; sometimes we have to say with Charles Mayo that it is not knowledge of anatomy and physiology which teaches us the significance of a certain pain, but experience with that same type of pain observed many times before, and what was found when the abdomen was opened. But in the majority of cases, the careful analysis of pain gives us valuable information and it may be the only solution to the diagnostic puzzle.

Are we trying to turn back the hands of the clock? I do not think so. We are simply repeating what Gowland Hopkins, the President of the Royal Society of London and the most distinguished research student in his own field, has said: "Experience at the bedside and the habit of close observation are essential for the making of a successful physician." We are simply stating that at the present writing the science of medicine alone, the results of clinical laboratory and x-ray studies, at least in the abdominal field, are not sufficient to lead to a correct diagnosis in most cases. It means we must not discard the art of medicine, and that the microscope, the test tube, the instruments of precision and the x-ray cannot as yet displace the eye, the ear, the finger, and the results of observation.

There is unquestionably too great a tendency at the present time to lean too heavily upon laboratory methods and too lightly upon pure clinical observation. If we recognize this imbalance and, while not neglecting the results of laboratory methods which are invaluable, attempt to recapture the marvelous clinical sense, the wonderful powers of observation, analysis and deduction of Bright and Addison and Sydenham, of Osler and Thayer, perhaps we may reach the point where we can say with Edmund von Neusser, the greatest clinician of his day, that: "The history of the case should give us our correct diagnosis; the physical examination and laboratory tests should be merely confirmatory"—or even be able to confirm what Hilton said many decades ago—"Every pain has its distinct and pregnant significance if we will but carefully search for it."

FACTORS INFLUENCING OPERATIVE MORTALITY IN EXOPHTHALMIC GOITER*

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During the past 50 years much has been written about the surgical management of patients with toxic goiter. Just before the introduction of iodine 12 years ago, the operative mortality had shown a steady reduction with increasing experience until, in the best clinics, it varied from 1 to 4 per cent. Not only had the mortality as a whole shown a marked reduction, but the mortality record of every thyroid surgeon had shown a marked decrease as his experience increased. This drop in the mortality rate may be attributed to two factors: (1) increase in surgical skill and improvement in technic; (2) improvement in surgical judgment. Surgeons gradually had learned when to operate and when not to operate and what surgical procedures their patients would tolerate. They had learned not to operate when the disease was increasing in severity, that the presence of marked emotional instability meant that it was unwise to attempt surgery, that the production of a gain in weight by the administration of a high caloric diet was a favorable sign, that psychic traumata exaggerated the disease and hence should be avoided, and that all of the signs and symptoms of the disease diminished in intensity with rest. Most surgeons moreover had agreed that it was wise to perform the thyroidectomy in several stages in the more severe cases. It is of some interest that, as a result of the application of these principles, the mortality in the clinics of the best thyroid surgeons was lower before the days of iodine than the mortality in many clinics at the present time.

Following the demonstration of the marked beneficial effects of iodine in exophthalmic goiter by Plummer, there was a tendency in some quarters to ignore the lessons learned before its introduction and to place too much reliance on iodine. It was said that iodine abolished crises and the need for multiple stage operations. It became rather common to say that the treatment of exophthalmic goiter consisted in the administration of iodine for about 10 days, followed by the performance of a subtotal thyroidectomy. It gradually became apparent, however, that some patients were still dying of typical thyroid crises after operation and that some patients died even before operative procedures could be carried out, in spite of the administration of large doses of iodine and the institution of other therapeutic measures known to be of value. The past few years have, therefore, been characterized by a growing realization of the importance of factors found

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to be of value before the days of iodine and by a more precise evaluation of the effect of iodine. The result is that we have come to regard iodine as a great help in preparing patients for operation, which must be used, not alone, but in conjunction with every other worthwhile therapeutic procedure.

The various factors of importance in the successful management of patients with toxic goiter may be discussed under the following headings:

1. The skill of the surgeon.
2. Selection of the time and type of operation, with special reference to emotional instability, iodine, diet and rest.
3. Treatment of complications.

1. *The Skill of the Surgeon.* In the successful outcome of all operative procedures surgical skill is a factor, and this is particularly true of thyroidectomies for exophthalmic goiter. In our experience, severe postoperative reactions and various complications of thyroidectomy have always been more common following surgical procedures carried out by inexperienced men than after those carried out by experienced men. We have repeatedly seen severe postoperative reactions follow hemithyroidectomies by inexperienced surgeons in patients that would probably have had mild reactions following subtotal thyroidectomies by experienced surgeons. We recall one young surgeon of little training who performed a thyroidectomy on a patient with exophthalmic goiter who had the disease in fairly mild form and in whom the emotional instability was not marked. From our observations, we predicted that the patient would have a mild postoperative reaction. Nevertheless, for 12 hours after operation, her pulse rate varied from 150 to 160 per minute and she was unduly sick. After this, and at about the time when the postoperative reaction usually becomes severe if it is going to, her pulse rate dropped markedly and she began to improve. Such a reaction we are inclined to attribute to direct trauma caused by unnecessary manipulation and prolongation of the operation through lack of surgical skill. We have pointed out elsewhere how the mortality rates of all prominent thyroid surgeons have steadily dropped with increasing experience. Men who become proficient in goiter surgery by doing large numbers of thyroidectomies over a long period will undoubtedly continue to have lower mortality rates than general surgeons who do a comparatively small number of thyroidectomies.

2. *Selection of the Time and Type of Operation.* It has been rather generally taught that a thyroidectomy should be performed as soon as the basal metabolism shows a maximum reduction, namely about 10 days after the administration of iodine is started. In recent years, we have departed somewhat from this dictum and have made it a point not to have patients operated on until we thought they were ready, regardless of how long operation needs to be postponed. It has been our experience that maximum improvement does not occur as soon as the basal metabolism has shown a maximum reduction, but only some time later, when the patient has had an opportunity to derive the benefit of the lowered rate of metabolism. In

gauging the ability of patients to withstand operative procedures, we pay most attention to the intensity of emotional instability. The severity of the postoperative reaction more closely parallels this factor than any other, a fact pointed out by Plummer years ago. If, in spite of a well marked reduction in basal metabolism, the patient still thrashes about in bed and weeps at frequent intervals, it is probably unwise to attempt operation. We have reported elsewhere [1] data on two patients which illustrate the importance of considering emotional instability. One was a girl of 17 whose basal metabolism was plus 108 per cent on admission to the hospital. With rest and iodine the rate dropped to plus 32 per cent and her pulse from 125 to 71. However, marked emotional instability persisted up to the time of operation. Laughing would alternate with weeping for no apparent reason. The morning of the operation she wept violently. She was operated on after the conventional period of iodine administration and had lost no weight after admission to the hospital. At no time during operation did her pulse rate rise above 88, yet she died 48 hours after operation of an intense thyroid reaction. A large thymus was found at autopsy which may or may not have been related to her death according to the Graves' constitution theory of Warthin [2] and others. The other patient was a man of 50 whose basal metabolism dropped only slightly (from plus 46 per cent to plus 33 per cent) during the administration of iodine. Although he gained 2.5 kg. in weight before operation, the nervous manifestations of the disease persisted in a severe form and we were skeptical about his ability to withstand surgery. Nevertheless, he took the anesthetic well and it was decided to proceed with a subtotal thyroidectomy. He died about thirty hours after operation of a thyroid crisis complicated by bronchopneumonia.

This raises the question of the importance of the basal metabolism in gauging the operative risk. On the average, the lower the basal metabolism the better the operative risk, but there are many exceptions to this rule. We have seen only moderately severe postoperative reactions in patients in whom the basal metabolism showed no reduction during the administration of large doses of iodine and remained at a level of from 50 to 60 per cent above normal, while we have seen other patients die whose basal metabolism was only from 20 to 30 per cent above normal at the time of operation. The first group of patients were comparatively calm and the second group unstable emotionally and it is the intensity of this factor which seemed to be related to the severity of the postoperative reaction.

Contrary to the generally accepted teaching, the basal metabolism will rise very little in most cases during the administration of iodine if operation is delayed from two to three weeks beyond the time of maximum reduction. The danger of a rise in metabolism during several weeks of treatment with iodine with the patient at rest in bed in the hospital, has, in our opinion, been overemphasized. If the metabolism does rise slightly we ignore it in gauging the probable outcome of the operation. In a few cases, however, the metabolism rises rapidly after an initial drop in spite of the administration of iodine

and sometimes to a higher level than before iodine was started. Associated with this rise in metabolism is an increase in the intensity of all the manifestations of the disease, including the nervous manifestations. Unfortunately this rise tends to occur in the patients who have the disease in the more severe form, that is in just those patients who need the benefit of rest most. This raises the problem of refractoriness to iodine and its management. We have reported elsewhere [3] two patients who became partially and completely refractory respectively to about 6 milligrams of iodine daily in the form of Lugol's solution during its prolonged administration and who, after periods of omission of from 30 to 60 days, again showed a well marked response to it. It has never been conclusively established that patients become completely refractory to much larger doses of iodine after showing an initial response, although it is likely that this occurs, because a certain percentage of patients initially show no response to iodine. The main problem is whether the refractoriness is caused by the iodine itself or by a spontaneous variation in the intensity of the disease. If the iodine is responsible, then it should be omitted, whereas if the nature of the disease itself is responsible, then iodine should be continued, because many patients develop only partial and not complete refractoriness to it. While this point is yet unsettled, we do know that if the metabolism is rising rapidly it is usually safe to omit iodine and that after a period of omission, patients will usually respond to it again. The administration of enormous doses of iodine (100 minims of Lugol's solution daily) during the refractory period is of no more value than the administration of much smaller doses, although teaching to the contrary persists. It is probable that 5 minims of Lugol's solution daily always produces a maximum effect. We have observed previously [4] about as much effect on metabolism in Boston during the administration of 1 minim of Lugol's solution daily as Lerman and Means [5] did during the administration of 90 minims daily. We routinely use 10 minims of Lugol's solution three times a day. This dose is used partly as a matter of habit and partly to prevent criticism on that score by surgeons when they have poor results. The form in which iodine is administered is not of great importance. Sodium iodide and potassium iodide possess the advantage over Lugol's solution that they are more palatable. Iodine has no effect on the secretion of the thyroid after it leaves the gland. It is, however, given routinely after operation because in a varying percentage of cases (from 5 to 15 per cent), depending upon the surgeon, enough thyroid tissue is left at operation to cause the disease to persist in a subdued form. Since it is impossible to predict at the time of operation just which cases these will be, it is necessary to administer iodine postoperatively to all patients in order to control the thyrotoxicosis in the few instances in which it persists.

Muscle weakness is one of the characteristic findings in exophthalmic goiter and when marked, as judged by inability to climb up on a chair without assistance, usually means that operative procedures will not be well

tolerated. Marked muscle weakness and marked emotional instability usually but not always go hand in hand. It is a matter of experience that these two manifestations of the disease, like all the others, usually decrease in intensity with rest. Thyroidectomies for exophthalmic goiter are not emergency operations and if done as such, kill a large percentage of the patients operated upon. We therefore, make it a point to delay operation until we think the patient will stand it. During this period we keep the patient in the hospital and continue the administration of iodine. Rest is not complete and the usual ambulatory privileges are allowed, except in the presence of extreme muscle weakness or cardiac decompensation.

We have virtually abandoned the ligation of arteries as a surgical procedure in exophthalmic goiter because it appears to have no influence on the course of the disease. Its only indication would appear to be to test the ability of the patient to withstand more extensive operative procedures when there is any doubt about this, and it should be possible to gauge this in other ways. It has the disadvantage that it produces unsightly scars and often renders more difficult the technic of a subsequent thyroidectomy. It is the impression of most workers in the field that the severity of the postoperative reaction is directly related to the extent of the surgical procedures, that is, the amount of tissue removed. Lahey [6] has said that hemithyroidectomies should be done in all patients in whom there is any doubt about the ability to withstand operation. Richter [7] does not agree with this point of view and feels that his low mortality, even before the days of iodine, may be attributed to the fact that he left very little thyroid tissue to cause any reaction. If, in spite of the various precautions outlined, the patient still seems to be in poor condition for operation, roentgen-ray treatment may be used. This has to be carried out with caution in severe cases. Although it may not cure the disease, it usually reduces its intensity sufficiently to permit a thyroidectomy to be done with safety.

It is important to bear in mind that exophthalmic goiter is a disease in which body tissue is broken down at a rapid rate. It is reasonable to assume that the prevention of this breakdown is a desirable therapeutic procedure. It has been our experience that a well marked gain in weight before operation is a favorable prognostic sign. If combined with a well marked reduction in basal metabolism a satisfactory outcome of the operation is almost assured. In order to make the patients gain weight, it is usually necessary that the caloric intake exceed the basal caloric expenditure by at least 100 per cent. This means that most patients should receive from 4000 to 5000 calories daily. Such a diet invariably assures an adequate protein intake to offset the high nitrogen excretion often present in the disease.

By administering a meal consisting largely of carbohydrate four hours before operation the danger of the development of acidosis shortly after operation is reduced. Such a meal may consist of 250 c.c. of orange juice and an average sized helping of oatmeal with milk. A dose of iodine

should be administered with the meal. Such a meal will usually be out of the stomach by the time of operation. For a few days following operation, the caloric expenditure of the individual, which was already high before operation, is still further accelerated. Hence the caloric intake should be maintained at as high a level as possible in the immediate postoperative period. This is usually most conveniently done by administering a mixture of equal parts of milk and cream, which should be begun as soon as vomiting ceases.

Patients who are in good condition before operation can withstand vomiting of from eight to 10 hours' duration without a serious drain on the body reserves. Should vomiting continue beyond this time, fluid should be administered subcutaneously in the form of 10 per cent glucose at the rate of 3000 c.c. in 24 hours. This not only provides fluid but prevents the development of an acidosis. The glucose should contain iodine in any suitable form. The patient should receive at least one dose of iodine in the 12 hour period immediately following operation. Rarely is it necessary or desirable to give fluid intravenously after operation. Whenever the circulation is so poor that fluid is not absorbed from the subcutaneous spaces, the condition of the patient is usually so critical that putting it directly into the circulation will not accomplish the desired result and has the further disadvantage of overloading the right side of a heart which is already failing. Moreover, when reactions occur, as they do occasionally even in hospitals where great care is used in the preparation of glucose, they are less apt to be fatal if the injection has been given subcutaneously than if it has been given intravenously. What has been said about the intravenous administration of glucose applies also to the intravenous administration of normal salt solution and various iodine preparations. The majority of patients do not require the parenteral administration of fluid. We have seen patients who were in excellent preoperative condition, and who otherwise would have had mild postoperative courses, suffer greatly because of reactions following the parenteral administration of fluid on a standing order. We know of several instances in which the needless administration of fluid by the subcutaneous and intravenous routes appeared to be a factor in the death of patients. In the postoperative management of our patients we deal with many different interns on many different services and our chief trouble is not to get them to do enough, but to keep them from doing too much.

3. *Treatment of Complications.* Cardiac Irregularities: The indications for thyroidectomy are virtually the same when cardiac irregularities are present as when they are absent. This means that in the absence of other untoward signs, we ignore cardiac irregularities in gauging the risk of operation. Auricular fibrillation in particular is common, both preoperatively and in the immediate postoperative period, and is of itself almost never a cause for alarm. Transient attacks of paroxysmal tachycardia are more serious, because of greater associated cardiac embarrassment. Actual cardiac decompensation at the time of operation, of course, increases the

risk considerably, although it is rarely necessary or advisable to carry out operative procedures when the heart is failing. It is still not definitely established whether digitalis and quinidine are of any value in the treatment of cardiac irregularities accompanying toxic goiter. Plummer still insists that digitalis is harmful and others, that it is a great help. We do not use digitalis in toxic goiter even in the presence of auricular fibrillation, because it has seemed to do no good and in some instances to embarrass rather than aid the heart. This applies particularly to the immediate postoperative period, during which some surgeons use it routinely for marked tachycardia with or without the presence of auricular fibrillation.

Tetany and Paralysis of the Vocal Cords: In the immediate postoperative period it is necessary to be on the watch for tetany and paralysis of the vocal cords. Tetany is comparatively rare and usually becomes evident on the second or third day after operation. When properly treated it is never fatal. It is rarely necessary to use the parathyroid hormone, calcium by mouth usually being sufficient. If an emergency arises, it can be controlled by injection of calcium intravenously. The main thing is to be constantly on the watch for tetany. Its incidence bears a direct relation to the extent of the surgical procedures, being more common in the more extensive operations. Since tetany is one of the most serious complications because it is usually permanent and there is no preparation of the parathyroid hormone which works indefinitely, we are skeptical about the wisdom of performing so-called total thyroidectomies which have been advocated by a few surgeons.

Paralysis of the vocal cords is fairly common and its incidence (from 5 to 15 per cent) appears to be related to the skill of the surgeon. In most instances it is unilateral but in rare instances is bilateral. In about half of the cases the paralysis is evident as soon as the patient awakes from the anesthetic, but in the other half does not become evident for from 12 to 36 hours after operation. It is usually associated with edema of the larynx which makes breathing difficult for from two to four days. This difficulty is relieved by inhalations of compound tincture of benzoin and a tracheotomy is almost never necessary even in patients with paralysis of both cords. It is most unusual for a vocal cord paralysis to be the cause of death following operation, although, by the increased muscular effort in breathing and the interference with sleep which it causes, the recovery of a very sick patient may be delayed.

It is of interest to see how the application of the principles outlined has affected the mortality from thyrotoxicosis in a large municipal hospital. Through the coöperation of Dr. Frederick Tice and other members of the staff, it has been possible to make a study of the disease at the Cook County Hospital in Chicago. Among the cases followed by other observers the mortality from thyroidectomies for exophthalmic goiter between the years 1931 and 1933 varied from 12.7 to 13.3 per cent, with an average mortality of 13.1 per cent (total of 305 cases). The mortality from toxic adenoma

during the same period varied from 8.1 to 12.1 per cent with an average mortality of 9.8 per cent (total of 102 cases). The average mortality for non-toxic adenoma during the same period was 4.1 per cent (106 cases) and for simple goiter, 2.6 per cent (38 cases).

In the patients with exophthalmic goiter whom we have personally followed during the period 1932–1934, the mortality has been 4.2 per cent (72 cases). The number of patients with other types of goiters is too small to base conclusions on, there having been 12 cases of toxic adenoma with no deaths and 14 cases of non-toxic adenoma with no deaths. It may be seen that the mortality among the patients with exophthalmic goiter that we have followed is the same as that in the group of patients with non-toxic goiter followed by other observers. The reduction in the operative mortality in exophthalmic goiter has been accomplished without any change in surgical personnel and without any significant change in surgical technic. In interpreting these data it must be borne in mind that the operative mortality in large municipal hospitals where all general surgeons of varying skill do goiter surgery can probably never be reduced to the level reported from highly specialized private clinics where only two or three men of unusual skill do all the thyroid surgery. Our mortality is still much too high and we hope to reduce it further, but at the present time it is probably as low as in any large city hospital and lower than in many of them.

This brings up the question of specialization in goiter surgery. In the training ordinarily considered adequate to prepare a man to do general surgery, so few goiter operations are performed that sufficient opportunity is not provided for the development of surgical judgment and skill. If institutions wish to reduce their goiter mortality to the lowest possible rate, they must be prepared to have all of their thyroid surgery done by only a few men who by experience have learned to appreciate the importance of adequate preoperative preparation of their patients and have developed speed and gentleness in their surgical technic.

It is of some interest to review briefly the case histories of the patients who died in order to consider how their lives might possibly have been spared. In the first patient the basal metabolism dropped from about plus 50 per cent to about plus 25 per cent during the administration of iodine although he did not gain any weight. The preoperative course of the disease was complicated by an upper respiratory infection which it was thought, however, had cleared up at the time of operation. The disease did not appear to be particularly severe. He seemed nervous as soon as he awoke from the anesthetic and his pulse rate for the most part was 140 or over thereafter. His temperature gradually rose to 105 just before death. It was possible to detect bronchopneumonia on physical examination 13 hours before death, which occurred 60 hours after operation. In the second patient the disease was complicated by diabetes. Although the metabolism was not very high (from plus 30 to plus 40 per cent), it did not show

any reduction during the administration of iodine. His preoperative course was also characterized by frequent attacks of diarrhea and a loss of 14 pounds in weight, caused by inability to get him to coöperate enough to eat the food ordered. He created the impression of being unable to stand much and his fellow patients had predicted that he would not survive the operation. Following the thyroidectomy he had a rather stormy course with a marked tachycardia and several insulin reactions. He appeared, however, to be doing fairly well three to four days after operation, only to become worse in association with the development of lobar pneumonia from which he died five days after operation. The third patient entered the Cook County Hospital August 1, 1933. Although his basal metabolism was only about plus 40 per cent, emotional instability and muscular weakness were well marked. During the administration of iodine his metabolism, instead of dropping, rose to about plus 58 per cent and the manifestations of the disease became more marked. It was felt that he could not stand a hemithyroidectomy and, against our advice, both superior poles were ligated September 11. Following operation his metabolism did not drop but he did lose five pounds. The inferior poles were ligated against our advice October 7. Again, his basal metabolism did not drop but he did lose another nine pounds and developed a paralysis of the left vocal cord. Iodine was omitted November 5, following which his metabolism rose to plus 70 per cent. He was sent home November 26 and reëntered the hospital January 3, 1934. When iodine was readministered his metabolism dropped only slightly to plus 60 per cent, but he did gain 13 pounds. A left hemithyroidectomy was done March 13, but it was greatly prolonged by the technical difficulty caused by the scar tissue from the first operations. His pulse rate rose from 110 to 160 during operation and remained at this level until three hours after operation when it became too weak to count. His temperature gradually rose to 103 and his respirations to 40. He became irrational six hours after operation and died an hour later.

In the first patient it is possible that operation was performed too soon after the upper respiratory infection. The second and third patients were not suitable risks for operation and it should either have been postponed still longer or an attempt made to reduce the intensity of the disease with roentgen-ray treatment before proceeding with surgery. The technical difficulties of operation contributed perhaps to the death of the third patient, but in these two deaths we ourselves must bear a large share of the responsibility, while in the death of the first patient the exact cause is uncertain. These deaths illustrate the main point, namely that operative mortality depends in large measure on the condition of the patient at the time of operation. The patient's life is saved in the preoperative period and very little can be done to avoid a fatal outcome after operative procedures have already been carried out. Success in the treatment depends upon intelligent cooperation between physician and surgeon.

Summary

The two most important factors in determining the risk of thyroidectomy for exophthalmic goiter are the preoperative condition of the patient and the skill of the surgeon. In preparing patients for operation great attention must be paid not only to the administration of iodine but also to the administration of a diet sufficiently high in calories to make the patients gain weight, to the control of emotional instability and to rest. The severity of the postoperative reaction appears to be related more directly to emotional instability than to any other factor. There should be no hesitation about postponing operation until the condition of the patient appears satisfactory.

Selection of the time of operation is more important than the selection of the type of operation, although the thyroidectomy should be performed in at least two stages in all patients in whom there is any doubt about the ability to withstand operative procedures. Ligations of arteries do not appear to affect the intensity of the disease.

Success in the treatment depends upon intelligent coöperation between physician and surgeon. Miracles can not be performed in the postoperative period and the time to prevent postoperative crises is in the preoperative period.

By applying the principles outlined to the preoperative treatment of exophthalmic goiter at the Cook County Hospital in Chicago it has been possible to reduce the operative mortality from 13 per cent to about 4 per cent without any change in surgical personnel or surgical technic.

In order to keep the operative mortality at the lowest possible rate, hospitals should not only pay more attention to the preparation of such patients for operation, but should relegate their thyroidectomies to a few surgeons who have developed good judgment, speed and gentleness and not to general surgeons who have had little opportunity to perfect the technic of thyroid surgery or to learn contraindications to operation.

We are greatly indebted to Dr. Frederick Tice and other members of the staff of Cook County Hospital for the privilege of making many of the observations referred to.

REFERENCES

1. Thompson, W. O.: Factors of importance in treatment of exophthalmic goiter, Illinois Med. Jr., 1932, lxii, 520–528.
2. Warthin, A. S.: Constitutional entity of exophthalmic goiter and so-called toxic adenoma, Ann. Int. Med., 1928, ii, 553–570.
3. Thompson, W. O., and Thompson, P. K.: Exophthalmic goiter; development of refractoriness to iodine, Arch. Int. Med., 1931, xlviii, 351–376.
4. Thompson, W. O., Brailey, A. G., Thompson, P. K., and Thorp, E. G.: Range of effective iodine dosage in exophthalmic goiter; effect on basal metabolism of rest and of daily administration of one drop of compound solution of iodine, Arch. Int. Med., 1930, xlv, 261–281.
5. Lerman, J., and Means, J. H.: Iodine in exophthalmic goiter; comparison of effect of ethyl iodide and potassium iodide with that of Lugol's solution, Am. Jr. Med. Sci., 1931, clxxxi, 745–755.
6. Lahey, F. H.: Management of post-thyroidectomy complications, Surg. Clin. N. Am., 1928, viii, 13–26.
7. Richter, H. M.: Thyroidectomy, Surg., Gynec. and Obst., 1929, xlix, 67–75.

THE ALTERNATIVE TO REVOLUTION *

By GLENN FRANK, *Madison, Wisconsin*

THE air is, at the moment, filled with premonitions of profound change in the political, social, and economic life of the United States.

Many Americans are sincerely fearful that we may rush into changes that will bring our traditional order of private enterprise and political liberty to a decisive and disastrous end. And they see no matured alternative around which grave doubts do not swarm. These Americans have no personal or political axes to grind by the expression of this fear. Their concern is genuine.

A few Americans, without this sincerity of concern, are attempting to further personal and partisan interests by branding even the simplest and most obviously sensible suggestion of change as part of a sinister plot to communize the nation. Save to express my contempt for such tactics, I shall waste no words on these ventures in shoddy politics and sordid economic propaganda. Sooner or later, the bogey-monger, whether hailing from the ranks of radicalism or reaction, is strangled by his own insincerity.

But, whether sobered by calm analysis or stimulated by faked alarms, the national mind is anxiously speculating on the turn affairs may take in the days ahead. Can we ride the storm without basic changes in the traditional order of American life and enterprise or are we in for a drastic reordering of our political and economic arrangements? I want to air this issue with as much candor and realism as I can muster.

No simple and single answer to this question is possible. The forces of change now in operation may be dammed up by inflexible tradition until they break the dykes with a rush of revolutionary energy or they may be directed by flexible intelligence into a process of social reconstruction that will give fresh significance and assured stability to our national future. Because I believe that the future and fortune of all of us now living will be determined by the outcome of the battle royal that is now on between the forces of inflexible tradition and the forces of flexible intelligence, I have chosen to chart the issues of this battle in terms of the current national situation.

I am convinced that profound historic change impends in the life and enterprise of our time. I am not at all sure of the direction this change will take. We may be in for a long retrogression or we may be on the threshold of renaissance. The blackening of the skies that began in 1929 may have heralded a permanent eclipse of the national genius or these may be but the grey hours before a social sunrise that will warm and illumine our lives where transient disaster has chilled and darkened them. In either case, the America of tomorrow will, I am convinced, be radically different from the

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America of yesterday's textbook or of today's newspaper. And what that America will be like will depend primarily upon whether the forces of inflexible tradition or the forces of flexible intelligence direct our affairs in the days immediately ahead.

Our national life is just now in the fourth phase of a sequence of events that has before in history brought whole peoples to the social crossroads where decisions affecting their destiny have had to be made. Unless I grossly misread the meaning of the last two decades of American history, four distinct developments have brought the American social order to its present critical juncture.

First, old philosophies and old procedures which had long dominated our political, social, and economic life fell into varying degrees of futility through the failures of American leaderships to keep them progressively adjusted to the new circumstances of this new age of science, technology, and plenty.

Second, while these old philosophies and old procedures were falling into futility, new philosophies and new procedures, more alert to the needs and better adapted to the nature of this new age, were being patiently and unobtrusively elaborated by scientists and seers whose historic mission it is to be the unofficial statesmen who, in freedom from the clamor of constituencies and the compulsions to compromise, blaze new trails of thought and action which the official statesmen may later follow if they will.

Third, a long period of manifest maladjustment between the old policies and the new problems of American life ensued, but, despite the heavy hand this maladjustment laid upon the lives of men, the masses of Americans clung uncritically to the doctrines of the fathers in matters political and economic.

Fourth, in the wake of the world-wide economic collapse, from one end of the United States to the other, men have been shaken out of the sterile serenity that marked their mood in the days of the pathological prosperity of the Coolidge era, with the result that today they no longer display reluctance to question even the major assumptions upon which their life and enterprise have long been organized.

It is the mood of this fourth phase that makes critical the present juncture in American affairs. The present temper of the American mind differs vividly from its pre-depression temper. In the days of our phantom prosperity we were sleek and self-satisfied. We were well-fed and wanted nothing so much as to be let alone. We were impatient of those queer persons who were forever raising disturbing questions about our political, social, and economic policies. As if anything could possibly be wrong with a civilization that was paying such excellent dividends! The result was that, throughout the prosperity period, we turned deaf ears to the advocates of political, social, and economic readjustments that might well have averted the disaster that has darkened our lives since 1929.

Even I, mild and modest commentator that I am, found myself damned as a dangerous citizen by certain Wisconsin politicians and a few Wisconsin industrialists, during the 1932 campaign, for having advocated ideas which have since been hailed as the soundest of sound business sense by that notoriously red organization, the United States Chamber of Commerce.

As long as the nation was on its economic joy ride, new ideas had hard sledding. Almost the sole exception to this was the lush growth of bootleg religions and the rise of an apostolate of fakirs who led thousands of otherwise intelligent Americans to believe that, in their wistful quest for the deeper meaning of existence, they could suck the juices of a living gospel from the dead rinds of ancient superstitions or the green stalks of bogus psychologies. It may be that mankind will always rebel in this irrational sort of way against an era that becomes so exclusively absorbed in the goods and chattels of a crass prosperity. At any rate, aside from this single exception of the gullible embracement of improvised religions, the American mind betrayed a baffling immunity to new ideas as long as the economic skies were bright. Until the chill and shadow of the market collapse fell upon us, we were smug to the point of blindness to the basic drift of our civilization. It would be difficult, I think, to put one's finger upon even a single truly productive new idea in politics or economics which swept the mass mind while the phase of prosperity was on.

An old Scotchman, seeking to account for this seeming immunity of the American mind to new ideas, said, "The heather was wet!" And anyone who has tramped over the hills of Scotland knows that when the heather is wet fires do not sweep easily across the fields. But today the situation is the exact reverse. The heather is not wet today. The heather is dry! Disillusionment has done its perfect work. The man in the street, along with the man in the furrow, is straining at the leash of old dogmas of politics and economics that have failed to keep hunger from his stomach, cold from his body, and fear from his heart. The tethers of a thousand traditional loyalties have slipped during the last five years as men have watched the very ground stakes of their social order loosen. And from one end of the United States to the other men are today fumbling blindly for some lead out of the blind alleys into which blind leaderships led them.

Such a mood is at once a grave danger and a great opportunity. A grave danger if irresponsible demagogy dominates it! A great opportunity if responsible statesmanship directs it!

In its present mood the mass mind is willing to follow responsible statesmanship. It would prefer to follow responsible statesmanship. It may follow irresponsible demagogy. And it lies wholly with statesmanship to say which turn affairs shall take.

The American mind, unless I grossly misread its present mood, will take counsel of its patience while a Roosevelt gathers power unprecedented into his hands and cuts the red tape that normally binds government to the hitching post of inaction. But it will not unduly prolong its patience. There is a latent impatience moving restlessly close under the surface of the liberal patience Americans generally have displayed during the difficult days of the last five years. The mass mind expects constructive action and creative results to follow the freedom to act which its mood made Congress make possible something more than a year ago.

And—let us speak plainly—the mass mind expects something more than a Red Cross statesmanship that momentarily salves the economic wounds of the time and subsidizes into transient silence a growing army of the legitimately discontented. It expects careful but courageous readjustments of our political, social, and economic policies that will enable us to take full advantage of the fruits of this new age of science, technology, and plenty.

It was for this, and this alone, that we adjourned so much that is traditional in our democracy. It was for this, and this alone, that we set up a crisis government under which a Roosevelt is given in peace time powers far beyond the powers given to a Wilson in war time. And the mass mind will hold this crisis government to strict accountability. If the fruits of this freedom to act, which the mass mood made possible, should fail visibly to ripen, the mass mind will turn inevitably to an alternative leadership. And the danger is that it might be none too discriminating in its selection of the alternative.

One thing should by now be clear, alike to the Roosevelt administration and to the political opposition, and that is this: We are past the point at which beating the tom-tom for obsolete traditions of politics and economics can either satisfy the mass mind or bring recovery and stabilization to our national life.

We still have time to choose between guided reconstruction and unguided revolt!

I use the word "revolt" instead of the word "revolution" because there is a basic difference between the two. This distinction was dramatized by the Duc de la Rochefoucald as he stood with King Louis watching the Parisian mob storm the Bastille in 1789.

"This is revolt," cried Louis.

"No, Sire," said Rochefoucald, "it is revolution."

Revolt was there, of course, but Rochefoucald was right in reminding Louis that he was watching the profounder process of revolution in which his people had set deliberately out to readjust the old tools of government, which were obsolete, to the new tasks of government, which were obvious. And this, as Rochefoucald saw, was a more fundamental thing than mere revolt. It was a far-reaching process of social readjustment in which revolt was but an incident that might or might not take place.

There can be revolt without revolution. There can be revolution without revolt. In fact, the greatest revolutions are not marred by revolts. We do not want revolt in the United States. And, unless the American intelligence wholly abdicates, we can face difficulties far more drastic than we have yet known without revolt. But, unless we are willing to run the risk of a lapse into complete social and economic chaos, we cannot avoid revolution, if by revolution we mean what we should mean, namely, evolution under the guidance of an intelligence that is neither enslaved by inflexible tradition nor dragged at the heels of ill-conceived change.

Changes are forever taking place in the life and enterprise of living

peoples. When change stops we may know that the genius of a people has gone cold and a civilization has died. We cannot escape the fact of change, no matter how stubborn our orthodoxies. The problem is not to prevent change but to pilot it to productive ends.

If flexible intelligence were always at the helm, we would keep our social institutions progressively adjusted to the changing circumstances that are inseparable from a living civilization. And the result would be that society would never come to dramatic turns in the road where it had to undertake wholesale readjustments of its policies to situations leadership had too long neglected. But, unhappily, this is not the way the race has functioned to date. There is always a lag between the swiftly changing life and the slowly changing institutions of a people. And it is this fact of lag that gives rise to the sort of crisis that has frozen the fountains of our enterprise for the last five years.

It is right that there should be some lag. Otherwise our institutions would be in a continuous St. Vitus dance of change that would make ordered life and productive enterprise impossible. We do not want our institutions to chase down the street after every Pied Piper who has snared a new notion from the cloudland of theory. Most new ideas are wrong. By which I mean that the race is lucky if experience ratifies as true one out of every thousand new theories it evolves. Most of the ideas that have survived the stress and storm of the centuries are right. I mean the ideas that have survived with vitality, not the ideas that have merely stayed on as cadavers to poison the intellectual atmosphere. All of which means that we must build our lives, individual and institutional, mainly on ideas the race has hammered out on the anvil of experience. No generation can expect to add more than a little to the wisdom of its ancestors.

It is not a matter of deciding whether we shall cling to tradition or cultivate change. Tradition and change are not alternatives. They are two indispensable elements of civilization that must be kept in the proper relation.

A certain amount of social lag is desirable in the interest of continuity and stability. We want our institutions to maintain a saving continuity. We do not want our churches, schools, and economic establishments taken to pieces every evening at sundown and put together again in some new pattern every morning at sunup. But we must remember that our institutions must maintain continuity with the future as well as continuity with the past. Otherwise they will some day find themselves tenantless and dark in the midst of a generation whose allegiance they no longer command. We want our institutions to have stability. But their stability must be the equilibrium of steadied action not of mere inertness. Otherwise they become but so much waste lumber cluttering the current scene. A certain degree of lag between institutional change and social change is, therefore, necessary if civilization is to be kept a going concern.

If, however, we permit the policies and procedures of our institutions, under the lordship of inflexible tradition, to lag too far behind the changes that are taking place in the society they were designed to serve, glaring maladjustments occur. These maladjustments produce a social instability. And this social instability may at any moment lead an otherwise patient people blindly to break continuity with the sound as well as the unsound values of the past.

This, I fear, is the pass to which we have permitted American affairs to come!

I have not come to this conclusion from reading the inflammatory manifestos of radical agitators. I have been driven to this conviction by such eminently respectable documents as the report of former President Hoover's Research Committee on Recent Social Trends. It is, I submit, impossible for any literate American to read the two major volumes of this Hoover report, together with the subsidiary volumes that elaborate its findings, without realizing that our American civilization has become, both in its nature and in its needs, a radically different civilization from the American civilization in terms of which our forefathers determined the major patterns and designed the major institutions of our political, social, and economic life. The resistless forces of physical science and industrial technology have completely remade the civilization going on outside the walls of our institutions. The problems that this changed and changing civilization is today putting to government, to business, to industry, to finance, to the church, to the school, and to the family, as these problems are assembled and analyzed in this Hoover report, are drastically different from the problems that faced us even a generation ago.

And the report of this Hoover committee dramatizes, as no document before or since has dramatized, the fatal lag between our old policies and our new problems. This monumental research in social trends boils down to this: most of the major patterns and most of the major institutions of our political, social, and economic life were designed in terms of an American civilization in which (1) the scale of enterprise was small, (2) the relationships of life simple, and (3) the tempo of affairs slow. But now these institutions must function in and serve an American civilization (1) in which the scale of enterprise is no longer small, but vast, (2) in which the relationships of life are no longer simple, but complex, and (3) in which the tempo of affairs is no longer slow, but swift.

The overshadowing problem of this generation is to keep the response of our institutions to the sort of sweeping changes reflected in this Hoover report a guided reconstruction without revolt. And I submit that nothing save a flexible intelligence, mediating wisely between the forces of tradition and the forces of change, can possibly insure this result.

I give you two immortal pronouncements, rich in statesmanlike guidance to a people, like ourselves, caught in the swirl of a rapidly changing civilization—one from John Stuart Mill, the other from Viscount Morley.

"The future of mankind will be gravely imperiled," said John Stuart Mill, "if great questions are left to be fought out between ignorant change and ignorant opposition to change."

This sentence might with profit be printed on the title pages of the 1936 campaign textbooks of both the Republican and Democratic parties!

"Great economic and social forces flow with tidal sweep over communities only half conscious of that which is befalling them," said Viscount Morley. "Wise statesmen are those who foresee what time is thus bringing, and try to shape institutions and to mould men's thought and purpose in accordance with the change that is silently surrounding them."

It is this emancipation from inflexible tradition and this exercise of flexible intelligence, expressed and exemplified by the John Stuart Mills and the Viscount Morleys, that constitutes the most crying need of this distraught time. It is this sort of judgment and action that the schools, colleges, and universities must prepare men to bring to those readjustments that have become imperative as a result of the silent but sweeping revolution that science and technology are working in the political, social, and economic arrangements of American life.

The question is not what we should think about some hypothetical "revolt" that the bogey-makers picture as stealing upon us unawares, like a thief in the night, hidden in the cloak of some professor who has had the insight to see and the courage to say that American capitalism must effect a sounder distribution of buying power if it wants to survive, or lurking in the surplice of some clergyman who has come to suspect that maybe war after all is not the whole will of God.

The question is what we purpose to do about the actual "revolution" through which the United States is now passing, the revolution induced by physical science and industrial technology, the revolution so adequately reported and ably documented by the Hoover Research Committee on Recent Social Trends.

It is no easy matter to bring flexible intelligence to bear upon public affairs in so confused a time. A thousand pressures—political, social, professional, and economic—come continually upon us to spend our energies fighting the windmills of imaginary threats of revolt instead of bringing our intelligence carefully but courageously to bear upon that guided reconstruction of American life which is, in my judgment, the only alternative to the increasing insecurity and ultimate collapse of our social and economic orders.

There are frightened reactionaries who are sure we are drifting into Communism. There are frightened radicals who are sure we are drifting into Fascism. We may, I think, take both these fears with a grain of salt. Nations never *drift* into either Fascism or Communism. Nations go Fascist or Communist only when the soil is thoroughly prepared for the seed and when there is behind the Fascist or Communist push a capable, clear-headed, closely knit, and rigidly disciplined group able to get its hands quickly on

the levers of military and economic power. There is nothing in the American picture to indicate that we have reached such a point. And there is nothing inherent in the situation that need ever lead us to such a pass.

We are not an easily inflammable people. Even the more moderate movement of American Socialism has not made dramatic headway during the last decade. In 1920, Eugene Debs polled more than 200,000 votes in New York State and more than 900,000 votes in the country as a whole. Twelve years later, in 1932, in a time of incredible economic hardship, when the wine of discontent was everywhere in ferment, the able and persuasive Norman Thomas polled only 175,000 votes in New York State and only about 800,000 votes in the country as a whole.

I am aware that, in 1932, a large protest vote, that might under more normal circumstances have gone to the Socialist candidate, went to Franklin D. Roosevelt. But that hardly argued the imminence of rebellion, for what has seemed to some the radicalism of Rooseveltian policies has come into the picture since the election. I submit, therefore, that both the low vote of Norman Thomas and the high vote of Franklin D. Roosevelt indicate that we are not an easily inflammable people. And, for this reason, I refuse to be stampeded by the alarmists.

I believe that the American tradition of private enterprise and political liberty, if now corrected in the light of experience and wisely adjusted to the new requirements of an age of plenty, will be in the forefront after all of us now living have long been dead and the Fascisms and Communisms of the moment have become the relics of dead yesterdays. I hope you did not overlook the " if " clause in that sentence, for candor compels me to say that I could not so confidently predict the survival of capitalism and democracy unless I made the prediction contingent upon our willingness to face fresh problems with fresh minds and to rethink and recast our basic policies respecting wages, hours, prices, profits, and control, as well as the processes of democratic self-government, in the light of the new circumstances of this new age of science, technology, and plenty.

The blunt truth is that the fate alike of private enterprise and of political liberty is wholly dependent upon the flexibility of intelligence we can muster in the decade immediately before us. There is no area of our common life—whether it be politics, economics, or religion—in which the current situation does not cry aloud for flexible intelligence.

Certainly flexible intelligence is needed in the field of politics. Political action has lately assumed a new importance for the American future. Donn Byrne, weaver of colorful tales of his beloved Ulster, once wrote, " I have never seen a government that brought heavier apples to the trees or heavier salmon to the rivers or a more purple heather and for this reason politics means nothing to me." Strange doctrine for an Irishman! It was doubtless temperament that led this Celtic prose-poet to assume so cavalier an attitude toward politics. It must be admitted, however, that, until lately, signs were not wanting that we might be passing out of the age of politics,

in the old sense of politics. The tone and temper, if not indeed the very structure, of our society were increasingly determined by non-political forces. Forces of physical science! Forces of industrial technology! Forces of cultural revaluation! These, rather than the decisions of politicians, were the forces that, for half a century, had been making, unmaking, and remaking civilizations throughout the Western world. And yet, at the moment, American destiny is, I am convinced, strangely dependent upon the quality of political thought and action we can contrive to bring to the direction of our industrial and international affairs in the days ahead.

We cannot expect more than transient and insecure phases of recovery until, as I have suggested, we have rethought and recast our basic policies respecting wages, hours, prices, profits, and control in terms of the new circumstances of this new age of science, technology, and plenty, and until we have achieved a rationalized program of world relations. I have been driven reluctantly to the conclusion that, as American life is now organized, we shall not find in the ranks of business, industry, and finance a leadership that can effect promptly enough and apply widely enough those basic readjustments of economic policy that events are forcing upon us as the price of recovery and stabilization, and that, for the time being at least, the initiative for these readjustments must come from political leadership, despite the dangers inherent in any undue extension of political sovereignty over private enterprise.

It is, I suspect, a flexibly intelligent political leadership, and it alone, that can break the impasse to which the forces of science and technology, in stubborn conflict with obsolete political and economic policies, have brought the American social order.

Certainly flexible intelligence is needed in the field of economics. I am singularly unmoved by the wolf cries of the Dr. Wirts who see a bolshevik behind every bush. But I am not blind to the fact that the fate of private initiative is definitely at stake in the whirl of affairs at Washington today. Individualism, rugged and otherwise, is on the run. This throws an unprecedented challenge to the sincere friends of private initiative. I count myself among the friends of private initiative.

I am not at all enamored of the prospect of having my own and the nation's life ordered about by bureaucrats. I should be reluctant to see the intricate processes of the nation's economic enterprise put at the mercy of the quality of intelligence that American politics has, by and large, been able to recruit during the last quarter century. I do not believe that the complex economic life of the United States can ever be run effectively from Washington. I doubt the wisdom of having political persons dictate in detail the risks and routines of American business and industry. And this doubt survives even the muddling mismanagement of the nation's enterprise by many of the leaders of business, industry, and finance in the decade before 1929.

But I am, I hope, a realist. And I set it down as a deep conviction that a sustained study of the passing show has forced upon me that if the freedom of private initiative dies on this continent in the next ten years its friends will have been responsible for its death because they failed to bring a flexible intelligence to its operation in the last ten years. For the last ten years, private initiative has been doing its level best to commit suicide. Under such circumstances, the more a statesman believed in private initiative, the more he would be moved to grab private initiative by the collar and seek to discipline it before it took the last fatal leap.

There is no dominant body of either Fascist or Communist thought in the United States. Franklin D. Roosevelt does not want to be a dictator. But neither an intelligent president nor an impatient people will stand idly by and see a whole civilization sink just in order to preserve the dogma of private initiative.

It lies, I think, with the leadership of American business, industry, and finance to say just how far infringements on private initiative shall permanently go in the readjustments imperatively before us. If the leadership of American industry will now pool its varied genius in a nationally integrated effort to work out and to put into effect as promptly as possible wage, hour, price, and profit policies that will spread the normal national income widely enough to make the toiling millions a dependable consumer market for the maximum output of our machine economy; if the leadership of American industry will make the increase, the enrichment, and the stabilization of life for the millions its first obligation; and if the leadership of American industry will expect private profit to come, as I think private profit should come, only as a by-product of and compensation for its statesmanlike administration of the social function of industry, neither the President nor the Congress will spend much time trying to fasten any dictatorship on American industry. And, incidentally, industrialists will find the size and the security of their total profits increased, even if the profit margin on the individual article or action is narrowed. If the leadership of American finance will produce a banking system that will serve instead of sink the nation's enterprises, no one will lie awake nights to devise halters and hobbles for bankers.

Nearly everybody in America prefers private initiative—if it will only deliver the goods. The economic disaster that has befallen us is not, in my judgment, inherent in the nature of private initiative, but is the result of its gross mismanagement. The preservation of private initiative will depend wholly, I think, upon its practitioners' bringing flexible intelligence to its operation in this new age of science, technology, and plenty.

Certainly flexible intelligence is needed in the field of religion if we are to preserve, as a sweetening and savoring factor in our national life, certain priceless values that are gravely endangered in this phase of social disillusionment. It may seem to some beside the point to inject the problem

of religion into this study of the social and economic renewal of American life. Let me tell you why I think it is not.

Despite the protestations of a few disgruntled politicians and short-sighted business men, the old order of catch-as-catch-can politics and economics is as dead as the dodo. The traditional order of American life and enterprise has come definitely to a cross roads where we must decide between a voluntary coöperation of all classes for common ends and submission to a regime of compulsion that will impose upon us political and economic arrangements that will break the stalemate of the last five years.

No authentic American wants to see compulsion come. The essence of the American spirit is its love of freedom. But there are only two regimes under which free men can survive: (1) the virtual anarchy of laissez faire, or (2) control through wide and willing coöperation. In a simple society laissez faire works well and free men enjoy stretching their powers unhindered. In a complex society laissez faire does not work well and sooner or later free men find their freedom worthless in the midst of a crashing collapse of their economic order.

Having practiced the virtual anarchy of laissez faire so long, free men, when caught in a collapse like the crash of 1929, rush distractedly about with next to no disciplined capacity for that prompt coöperation for common ends which the enterprise of recovery and stabilization requires. And, in their distraction, they all too often fall wistfully into the arms of dictatorship. This is the story of Italy. This is the story of Russia. This is the story of Germany. This may become the story of France. This may happen in England. Will this be the story in the United States? It may!

There is just one thing that will prevent our surrender to an increasing compulsion. And that is a nation-wide crusade, essentially religious in its passion and purpose, for the universal coöperation of individuals, groups, and classes in the determination of policy in terms of the common welfare of the whole nation. The total combined forces of Catholicism and Protestantism, augmented by all the anonymous religious concern that may reside in our people, should now be brought to focus on the stimulation of a vigorous faith in and active effort toward a nation-wide reconsideration and redirection of our political, social, and economic orders through a vast popular coöperation in which personal and class interests are adjourned and the increase, enrichment, and stabilization of life for the millions made the dominant concern.

Until the economics of a New Deal are fortified by the religion of a New Deal, we shall continue to be victimized by the predatory trickeries of the trader and the polite treasons of the politician. And this social passion for the common welfare of the nation must be more than a crusade for secular uplift. It must sink its roots in the soil of a faith that lies beyond economics. The future of American religion and the future of the Ameri-

can social order are more intimately interlocked than many, in the facile modernism of their reasoning, have been inclined to think.

It is disclosing no secret to say that the fountains of religious concern have tended to go dry while for the last half century we have wandered in the far country of materialism, concentrating our energies upon laying the physical foundations and elaborating the instruments of our machine economy which today stands stalled in our presence.

Many are rightly concerned over the widespread secession from belief in God that has been increasingly evident as the machine age has come to maturity. I know the barbarisms and indignities that fanatics have perpetrated in the name of God. I know the innumerable caricatures that short-sighted men have drawn of His countenance, reading their own lusts and limitations into His purposes. I know how often whole peoples have projected either the tyranny or the tenderness of their social orders into their concept of God. I know how often sinister interests have sought to use God as a smoke screen for their anti-social adventures. But I know also the myriad army of saints and seers whose lives, illuminated by the light of His countenance, have been given to fertilize the soil from which the freedom, as well as the faith, of the race has flowered. And I am convinced that a civilization that exiles an exalted concept of God from its heart dries up one of the major well-springs of its power.

I agree with the sometimes exquisitely pagan Edna St. Vincent Millay when she writes:

> Not Truth, but Faith, it is
> That keeps the world alive. If all at once
> Faith were to slacken—that unconscious Faith
> Which must, I know, yet be the corner stone
> Of all believing—birds now flying fearless
> Across would drop in terror to the earth;
> Fishes would drown; and the all-governing reins
> Would tangle in the frantic hands of God
> And the worlds gallop headlong to destruction.

Remote as their relation may seem to the practicalities of social and economic renewal, here are questions quite as vital to the national future as industrial codes and tariff agreements: How shall the forces of religion make God again believable to men who have lost all faith in any lordship of life? How shall we save men of this generation from a corrosive cynicism? How shall we help disillusioned men to recapture a courageous confidence that life is not just a blind dance of atoms, but a meaningful adventure worthy of deathless objectives?

I shall not presume to make any final answer to these questions that have harrassed mankind since the infancy of the race. But of one thing I feel sure: few, if any, men are drawn to belief or driven into disbelief in God by the traditional dialectics of the theists and atheists. Men's belief in God is broken or buttressed less by the arguments they hear than by the

way in which the social order, in which they have to live, breaks or buttresses their lives.

A man whose life has been broken by the brutality of his fellows is less likely to believe in a beneficent God. "Friends should be kind to a despairing man," Job is found to say in one of the modern translations of the Old Testament, "or he will give up faith in the Almighty." And Johan Bojer, in his "The Great Hunger," makes an old Norwegian farmer say, "I sowed my enemy's field with corn in order that God might continue to exist." And, from an ancient scripture and a modern tale, I bring you the conviction that men's belief or disbelief in God may be but a reflection of what society has done to their lives. If we compel a man to live his life in a social order bereft of love and its sterner counterpart, justice, we must not be surprised if he has difficulty in believing in a God of love and justice. We cannot expect a God of love to be wholly convincing in a loveless world. And to ask men to believe in a God of justice when their whole lives have been blighted by injustice is, to say the least, optimistic.

Men of flexible intelligence, concerned to renew and release the religious impulse as a factor in the reinvigoration of our national life, will not attempt to combat atheism or to cultivate a belief in God by sheer dialectics. For men of flexible intelligence will know that the future of religion on this continent depends less upon the explanations of professors and the exhortations of parsons than upon the kind of social order we build on this continent.

All of which means that, if the future of the social order is influenced by the quality of religion, the future of religion is also influenced by the quality of the social order. If we are to achieve a balanced and meaningful civilization, therefore, we must work concurrently for the revitalization of religion and the reconstruction of the social order.

And now my argument draws to a close. I have exalted the virtue of flexible intelligence as the one hope of a stable and significant national future. It remains only for me to say that, in my judgment, the stimulation and discipline of this flexible intelligence is the supreme contribution the schools, colleges, and universities can make to this disordered and distraught time. Need I say that schools, colleges, and universities cannot stimulate and discipline this flexible intelligence unless they are themselves left free to bring flexible intelligence to bear upon the problems with which they must deal? Yes, I think it must be said, for we may be running into a time in which greater pressures than ever before will be brought to bear upon the schools, colleges, and universities to mould them to a pattern, to soft-pedal their researches into living realities, to tell them what they may and may not say.

There are three major systems of political control now functioning in the Western world—Fascism, Communism, and Democracy. Fascism and Communism have decided what they will do with their schools. They have decided that the laboratory must take orders from the legislature. There

are no dissenting professors in Italy. Dissenters have either suffered exile or bought their posts at the price of silence. There are no dissenting professors in Moscow. They are either nursing their wounds in Paris or picking up a precarious living as best they can elsewhere in the Western world. And now Hitler has put the sign of the Swastika on German scholarship. As Charles E. Merriam has suggested, it remains only for the democracies of the West to say that they will not tolerate differences of opinion to make it unanimous, and then we can blow out the light and fight it out in the dark, for, when the cry of intelligence is silenced, the rattle of machine guns begins.

EDITORIALS

CONTROL OF MEDICAL PRACTICE

Fairness, it would seem, demands, in any human transaction, that the rights of all parties shall receive due consideration. This principle should apply to the doctor-patient relationship, which is in effect the sale (when it isn't a gift) of medical care to the patient by the doctor. Both parties to the transaction are deeply interested. To the patient, it may be a life or death matter; to the doctor, a portion of his livelihood. Exploitation of either by the other is incompatible with sound ethics. Yet we have it on high authority that " all features of medical service in any method of medical practice should be under the control of the medical profession. No other body or individual is legally or educationally equipped to exercise such control." The patient is to take what he can get and be thankful. So-called organized medicine, an interested party, is to be the sole arbiter of how the public, the other interested party, can obtain its medical service. The public is to have no voice in the matter. The medical profession does not admit that anyone can tell it anything about these matters. Such an attitude by " organized medicine " is explicable only on the theory that the fear of state medicine has given it the jitters.

The statement that none is equipped educationally or legally to exercise control over medical service save the doctor will have to be supported by evidence. One might even question whether the doctor himself is fully equipped. What, for example, does he know in any expert way of the economic and social factors that enter into so complex a problem as the rendering of adequate medical care to the whole community? How much does he know of the prevention of disease? Precious little, and it will make a bigger hit with the public if he admits this and seeks advice, than if he assumes an attitude of omniscience. Even in the biologic aspects of his applied science, the physician leans heavily on the pure scientist, the physiologist, the biochemist, the physicist and others. Why should he not do likewise in the social? Perfection in the technic of any human enterprise is approached by the coöperation of all persons who have any intellectual contributions to make toward it. Improvement in supplying the community with medical care will be made by the collaboration of persons of varied interest, the health officer, the nurse, the social worker, the economist, the business administrator and others, as well as the man of medicine. Moreover, the public, that is to say the patient taken collectively, has a right to be heard.

Improved methods of rendering medical service, like advances in the science of medicine or any other science, will be found by experiment. Various types of medical practice, group practice, contract practice, industrial medical services, group prepayment plans, health insurance and any

others that seem to offer some promise, must be tried out. If experience shows them undesirable, they will naturally languish and die. It is to be remembered that a type of service that is suitable in one locality, or for one group of people, may be totally unsuitable for another. There must be a high degree of adaptability on the part of medicine, organized or unorganized, to meet various needs. In so far as it genuinely seeks to find better ways of furnishing medical care, it will gain public confidence: in so far as it adopts an attitude of fearsome standpattism, it will lose it. The profession ought always to remember that the doctor exists for the patient, not the patient for the doctor.

J. H. MEANS

AN ADVANCE IN THE DIAGNOSIS OF LEAD POISONING

The diagnosis of lead poisoning by its symptoms and by the signs found on physical examination is usually uncertain and needs for its confirmation a history of exposure to lead and the additional evidence procurable by laboratory tests. In adults the history of exposure to lead may be quite obvious as, for example, in those cases which arise among workers burning off lead paint with torches in enclosed spaces; or the determination of exposure may require considerable technical knowledge of industrial processes and not a little detective ability. The running down of the cause of a recent small epidemic in which the source of lead exposure was found to be the burning in stoves of discarded wooden battery casings impregnated with lead salts is an instance of the keenness that may be required in such an inquiry. In infants and children the patient may be able to give no assistance, and unless the physician is well aware of the frequency of lead poisoning at an early age he may not obtain from others the history of gnawing paint from window-sills or from toys, or of eating enamel flakes from cribs that would throw another light on the diagnosis of brain tumor, epilepsy, or appendicitis suggested by the symptoms.

The frequent lack of decisive symptoms, signs, or history in cases which nevertheless suggest the possibility of lead poisoning lends especial interest to any advance in the detection of lead poisoning by laboratory tests.

It was observed many years ago that the stippling of red cells exhibited a certain parallelism with the symptoms of active lead poisoning; and this simple laboratory method, that of studying the stained blood smear for stippled cells, remains one of the most valuable diagnostic measures. Stippled cells are, however, absent in as high as 30 per cent (Park) of cases of lead poisoning, and because of this inconstancy and because of a desire for a more quantitative method, the study of lead in the excreta and in the body itself has been pushed in recent years.

A primary difficulty arises from the fact that the presence of lead in the body or in the excreta proves only that exposure to lead has occurred and not that the defense mechanisms of the body have been overcome so

that active lead intoxication is in progress. Ingested lead may be held for the most part in insoluble forms in the digestive canal, and the presence of even considerable lead in the stools is not certain proof of lead absorption or intoxication. Lead excreted in the urine is, of course, derived from the lead in the blood stream and it may be assumed that its amount is usually roughly proportional to that of the circulating lead. The amount of circulating lead is undoubtedly the most important factor in determining whether or not damage to susceptible tissues will occur. The quantitative determination of lead in the urine should therefore be of great assistance in deciding the question of the presence of active lead poisoning. Certain difficulties, however, detract from the value of the method. In the first place, individuals exposed to lead may successfully store lead in their bones as rapidly as it enters their blood streams; they are instances of what might be termed compensated as opposed to active lead poisoning. The level of lead in their blood streams perhaps never reaches the height necessary to produce injury to susceptible tissues. Yet there is constantly some lead in their blood streams and constantly some lead excreted in the urine. Now the difference between the amount of urinary lead in such a case and in a case of active lead poisoning is usually less than a milligram in a 24 hour period. The necessary delicacy of chemical technic to dependably demonstrate difference of this order in the amount of urinary lead is not readily acquired. The method is valuable, therefore, when available, but for the majority of cases it is inapplicable because technical difficulties and expense have barred it from most laboratories.

The most positive evidence of active lead poisoning would evidently consist of quantitative analysis of the blood which would indicate the presence of an amount of lead incompatible with mere compensated lead poisoning. The amount of lead in the blood is too minute for present chemical methods. The application of spectographic analysis to blood ash has, however, proved fruitful (Shipley, Scott and Blumberg [1]) and the results of this method so far constitute a distinct step forward. The delicacy of the method is so great that the absence of lead bands in the spectogram constitutes definite evidence of the absence of circulating lead. If lead bands are found an absolute quantitative estimation of the amount of lead present cannot be made, but there appears to be a difference in intensity which can be made use of in distinguishing between compensated and active cases of poisoning.

From a practical point of view, the new method has both difficulties and advantages. The expense of the apparatus and the necessary skill and experience for its use and for the interpretation of results will rule out the method for routine use in hospital laboratories. On the other hand, the manipulations involved in a single test are infinitely less time-consuming than are those needed for a quantitative chemical determination of lead in

[1] Shipley, P. G., Scott, T. F. M., and Blumberg, H.: Spectographic detection of lead in blood as aid to clinical diagnosis of plumbism, Bull. Johns Hopkins Hosp., 1932, li, 327–328.

the urine. A large city might be served by one apparatus in a central laboratory. The result may be obtained more quickly than by chemical methods, and it would appear that since the possible sources of error are less numerous the result should be more dependable. Research in the mechanisms of lead poisoning will be aided by the development of this analytic method which is applicable not only to the blood and other fluids but to the solid tissues of the body as well. Its use as an aid in the clinical diagnosis of lead poisoning will no doubt rapidly become general.

REVIEWS

A Diabetic Manual. By ELLIOTT P. JOSLIN. Fifth Edition. 224 pages; 14 × 20.5 cm. Lea and Febiger, Philadelphia. 1934. Price, $2.00.

This small volume is so widely known to the profession as to need only brief review. To those who have not employed it in their practice it may be highly recommended, especially for intelligent patients. It is written so as to present to the patient, and incidentally to his physician, the more important facts concerning diabetes: the factors predisposing to it, its symptoms, course, complications, prognosis, relationship to marriage and pregnancy, and the various aspects of its treatment by diet and insulin.

However, it is not only facts that Dr. Joslin presents, but a religion for the diabetic. To adhere rigorously to treatment in order to live longer is shown to be the diabetic's duty not only to himself but to other diabetics who will be encouraged to do likewise. The author's enthusiasm leads him into a peculiarly personal method of presentation. He pleads the cause of optimism for the diabetic and goes at some length into the statistical basis for optimism. Pictures of vigorous youngsters with diabetes are freely used. Short case histories are presented to illustrate the results both of good treatment and neglect of treatment. There is no other manual for diabetics which does so much to develop the morale of the patient.

M. C. P.

Some Modern Extensions of Beaumont's Studies on Alexis St. Martin. Beaumont Foundation Lectures. Reprinted from the *Journal of the Michigan State Medical Society*, March to May, 1933. By W. B. CANNON, M.D., S.D., LL.D., George Higginson Professor of Physiology, Harvard Medical School. 87 pages; 13.5 × 20.5 cm. Wayne County Medical Society, 4421 Woodward at Canfield. Detroit. 1933.

The Twelfth Series of Beaumont Foundation Lectures commemorated the one hundredth anniversary of the publication of William Beaumont's classic "Experiments and Observations on the Gastric Juice and the Physiology of Digestion." As lecturer, Dr. Cannon chose to compare modern knowledge of certain phases of digestive physiology with Beaumont's observations in these same fields. The three lectures deal with "Thirst and Hunger," "The Important Relations of Digestion and Health," and "Digestive Disturbances Produced by Pain and Emotional Excitement." They constitute interesting and clearly presented accounts of advances in these fields but are not complete surveys of present knowledge, and do not present any new concepts.

M. C. P.

Practical Methods in Biochemistry. By F. C. KOCH, Professor of Physiological Chemistry, University of Chicago, vii + 282 pages; 16 × 23.5 cm. William Wood and Co., Baltimore. 1934. Price, $2.25.

For some time physiological chemistry departments have found it necessary to formulate manuals of their own for all laboratory work, which involved considerable time and expense. This laboratory manual should fill this deplorable want for such books. Although the author has intended this as the "practical companion" of Professor A. P. Mathews' textbook, it can be used with ease with any text desired.

The manual is arranged in three parts: the chemistry of cell constituents, the chemistry of the digestive tract and blood and urine. These are in turn divided into

chapters dealing with individual subjects. The experiments are preceded by brief discussions of the chemistry involved, including references to the original articles Dr. Koch has not been sparing in the number of experiments presented, so that it is possible to make a choice of those that seem more pertinent for the particular course offered.

The manual is modern in every sense of the word, for the author has rejected in some parts old and customary experiments for those that have but lately been presented in the journals. This is rather markedly illustrated by the introduction of methods for quantitative glucose determinations in the urine other than the standard Benedict's quantitative test. For the most part, however, the old methods, with improvements if possible, are included along with the newer ones.

The appendix is complete with instructions to the student as to laboratory procedures and technic, with discussions as to normal and molar solutions and with methods for preparing all solutions.

Finally, it is a splendid book of its kind, up to date in its material and complete in its discussions and directions.

E. M. R.

Recent Advances in Pathology. By GEOFFREY HADFIELD, M.D., F.R.C.P. (Lond.), and LAWRENCE P. GARROD, M.A., M.D., B.Ch. (Camb.), M.R.C.P. (Lond.). xii + 457 pages; 15 × 21 cm. P. Blakiston's Son and Co., Philadelphia. 1934. Price, $4.00.

The second edition of this excellent little book has been issued within two years of the first. It contains a number of additions, notably an elaboration of the authors' reasons for looking upon the major forms of anemia as primarily due to disorders of gastrointestinal function.

It is evident that judgment as to the relative importance of advances in a field as broad as that of pathology is bound to be an individual matter. The authors have made a very catholic selection of topics for discussion, grouping them partly under the systems of the body, and partly under such general headings as the reticulo-endothelial system, the deficiency diseases, the ductless glands, etc.

The discussion of the recent advances in our knowledge of cancer constitutes a valuable summary of this subject divided into chapters on carcinogenesis by irritants, the transplantation of tumors, tumor metabolism, heredity, and therapeutic cancer research. The authors have a gift of clarity of style and of concise statement, which enables them to present the complex and confusing data in this field in a clear and highly interesting way. The critical analysis of the experimental evidence adds a great deal to the value of this section. The treatment of other topics is much briefer than that devoted to the cancer problem, and though most of the sections are adequate and stimulating certain of them suffer from too great condensation. This seems true, for example, of the discussion of anoxemia which will probably seem clear only to those who are already reasonably acquainted with the subject. The statement made on page 241 that "the respiratory center responds not to a reduction of oxygen in the circulating blood but only to an increase of CO_2," is misleading. The discussion of recent work on pneumonia is even more inadequate. The types of pneumococcus are considered, but the discovery of the specific capsular polysaccharides and Avery's work on the enzyme destruction of the Type III polysaccharide are not mentioned.

The task as a whole, however, is well performed; a very clear and critical summary of many of the chief advances in the field of pathology is presented in brief form. It is a book worthy of repeated editions. The illustrations are excellent, the references well chosen. Internists will find it readable, instructive and stimulating.

M. C. P.

The Dangerous Age in Men. A Treatise on the Prostate Gland. By CHESTER TILTON STONE, M.D. 105 pages; 14 × 20 cm. The MacMillan Company, New York City. 1934. Price, $1.75.

In the reviewer's opinion this book should not have been published by a reputable firm. It is the type of pseudo-scientific description of the relation of the sexual glands to sex life and to health in general that is particularly apt unnecessarily to alarm the layman for whom it is intended. According to the author, the disorders and diseases of the prostate are, with few exceptions, the commonest affecting adult males, but "by properly caring for this organ, the entire body becomes like a car brought up to date." He feels that it is safe to say that 60 per cent of all men past 40 have trouble with the prostate gland and "deferring old age resolves itself either into keeping these glands fit or into bringing them back to their proper function." "Since without sexual power there can be no real bodily and mental strength or capacity this power must be kept in a state of efficiency by the regular and proper exercise of the sexual functions." On page 51 a case is cited to support this need of intercourse. A widower develops prostatic symptoms and is advised to remarry. Failing compliance in this or in medical treatment it is stated that "the prostate would have gone on swelling until finally a tumor of the prostate developed."

The several chapters on the horrors of prostatitis, seminal vesiculitis, etc., are not only full of exaggerated and incorrect statements, but are calculated to give to laymen an entirely false idea about the efficacy of local treatment of the prostate. The book as a whole constitutes an abuse of the physician's privilege of advising the public.

M. C. P.

Medicine, a Voyage of Discovery. By JOSEF LÖBEL; translated from the German by L. MARIE SIEVEKING and IAN D. MORROW. 334 pages; 15.5 × 22 cm. Farrar and Rinehart, Murray Hill, New York. 1934. Price, $3.00.

Here are 16 essays telling the story of medicine in a somewhat different way from that ordinarily used. The first and last articles are on medicine and the others take up biology, anatomy and the other branches of the healing science and art. It is a book written by a man of wide learning and true culture who appreciates how medicine came into being and what it really is all about. The book is well translated and conveys the charm which must characterize the original. There is a slip by the translators who use the word typhus where they should have employed typhoid but it is a natural one considering the term as it is used in German.

The author does not give the earlier physicians their due. He fails to mention Minot in connection with the account of pernicious anemia, contenting himself with setting it down as an American contribution. There are a few other omissions of the same nature. He spells the anatomist Monro's name with an *e* added and leaves one a little confused as to where the resurrectionist scandal took place. These are in themselves small matters, for the book is a fine one, suited for medical men and particularly for medical students and nurses, to say nothing of the well educated layman. It will make a most acceptable Christmas present.

J. R.

COLLEGE NEWS NOTES

Gifts to the College Library

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Major J. R. Darnall (Fellow), Ancon, C. Z.—2 reprints.

Dr. Ralph W. Mendelson (Fellow), Albuquerque, N. M.—1 reprint.

Dr. Oscar W. Bethea (Fellow), professor of therapeutics, Graduate School of Medicine, Tulane University, New Orleans, La., delivered the commencement address at the one hundred and twelfth annual commencement of the Philadelphia College of Pharmacy and Science during June. He was the recipient of the honorary degree of Master of Pharmacy from the College, as was also Dr. Walter Bastedo (Fellow), of New York City.

Dr. Edgar Erskine Hume (Fellow), Major (M. C.), U. S. Army, was the recipient of the honorary degree of Doctor of Laws at the last annual commencement of Georgetown University.

Dr. David P. Barr (Fellow), St. Louis, Mo., has been giving a course of lectures on diseases of the endocrine glands at the University of Melbourne, Australia, during the past summer.

Dr. Frederick H. Lamb (Associate), Davenport, Iowa, is the newly installed president of the American Society of Clinical Pathologists.

Dr. Kennon Henry Dunham (Fellow), Cincinnati, Ohio, is the newly elected president of the National Tuberculosis Association.

Dr. James P. Leake (Fellow), senior surgeon, U. S. Public Health Service, has been relieved from duty in the division of sanitary reports and statistics and assigned to duty in the division of scientific research, effective June 23. He is in California coöperating with health officials in combatting the recent outbreak of poliomyelitis.

Dr. Frederick K. Herpel (Fellow), West Palm Beach, Fla., is the newly elected president of the Florida Radiological Association.

Dr. Howard T. Karsner (Fellow), Director of the Institute of Pathology of Western Reserve University, Cleveland, Ohio, will attend the triennial conference in Europe of the International Society for Geographic Pathology, meeting in Utrecht, Holland, of which he is a member of the Directoral Committee of five members. Later he will visit laboratories in London and Cambridge, England, Hamburg and Freiburg, Germany, and Strasbourg, France.

Dr. William H. Walsh (Fellow), hospital consultant, of Chicago, sailed July 21 for Leningrad, where he will make an independent study of health and hospital conditions and practices in the U. S. S. R. Dr. Walsh's itinerary will take him to Leningrad, Moscow, Kharkov, Odessa, Kiev and Minsk, returning in September via Warsaw, Berlin and Paris.

Dr. B. S. Pollak (Fellow), Medical Director of the Hudson County Tuberculosis Hospital and Sanatorium, Secaucus, N. J., has announced the initial work on the construction of a new 25-story tuberculosis hospital.

Dr. Grafton Tyler Brown (Fellow), Washington, D. C., was recently elected president of the Georgetown Clinical Society.

Dr. Alexander B. Moore (Fellow), Professor of Roentgenology at the Georgetown University School of Medicine, Washington, D. C., delivered the Russell D. Carman Memorial Lecture on "Function of the Roentgenologist in the Diagnosis of Intra-Abdominal Conditions" at the eighty-first annual session of the Minnesota State Medical Association held in Duluth, July 15 to 18.

Dr. Willard Cole Rappleye (Fellow), Dean of Columbia University College of Physicians and Surgeons, has been appointed Dean also of the School of Dental and Oral Surgery, beginning July 1.

Dr. Bailey K. Ashford (Fellow), retired Colonel of the Medical Corps of the U. S. Army, has just published an autobiography, "A Soldier in Science." A dinner in honor of Dr. Ashford was held at the Harvard Club, June 27, sponsored by New York physicians and officials of the Pan American Medical Association, in recognition of his contributions to tropical medicine.

Dr. Hillyer Rudisill, Jr. (Fellow) has been made Professor of Roentgenology in the Medical College of South Carolina.

The National Research Council has announced the following grants in the field of medical sciences to Fellows of the American College of Physicians:

Dr. John A. E. Eyster, Professor of Physiology, University of Wisconsin Medical School; the electrical field around the contracting heart and skeletal muscle and related phenomena.

Dr. Frank A. McJunkin, Professor and Head of the Department of Pathology, Bacteriology and Preventive Medicine, Loyola University School of Medicine, Chicago; extraction and purification of agents that inhibit mitotic proliferation in the kidney.

Dr. Edward B. Krumbhaar (Fellow), Philadelphia, was elected President of the American Association of the History of Medicine at its last annual meeting in Cleveland, June 11.

Dr. William S. Middleton (Fellow), Madison, Wis., was elected a Vice-President, and Dr. E. J. G. Beardsley (Fellow), Philadelphia, Secretary.

Dr. Alfred Friedlander (Fellow), Professor of Medicine, University of Cincinnati College of Medicine, has been appointed Dean of the College to succeed Dr. Arthur C. Bachmeyer, resigned. Dr. Friedlander will assume office September 15.